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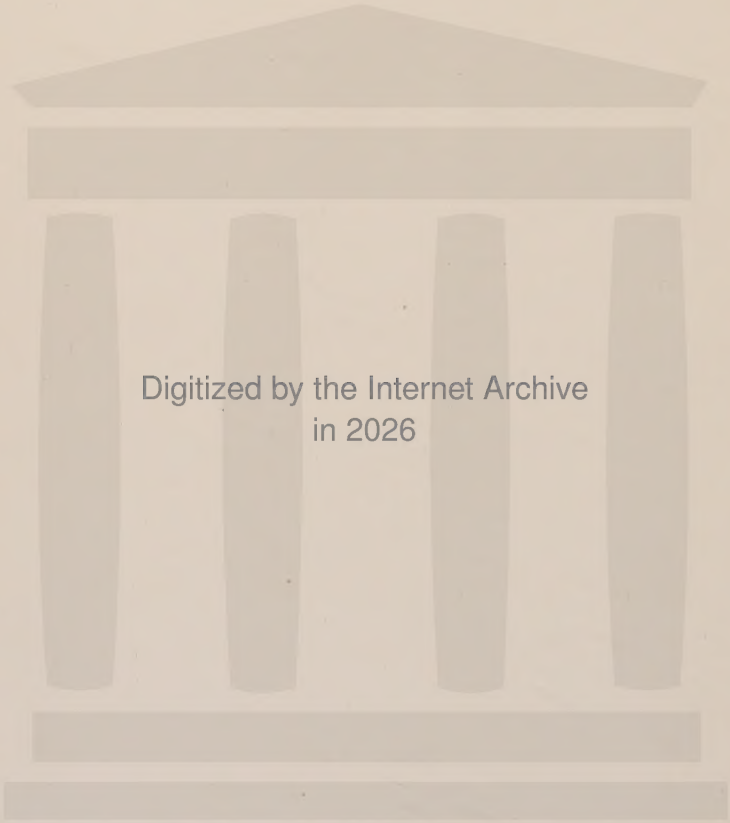
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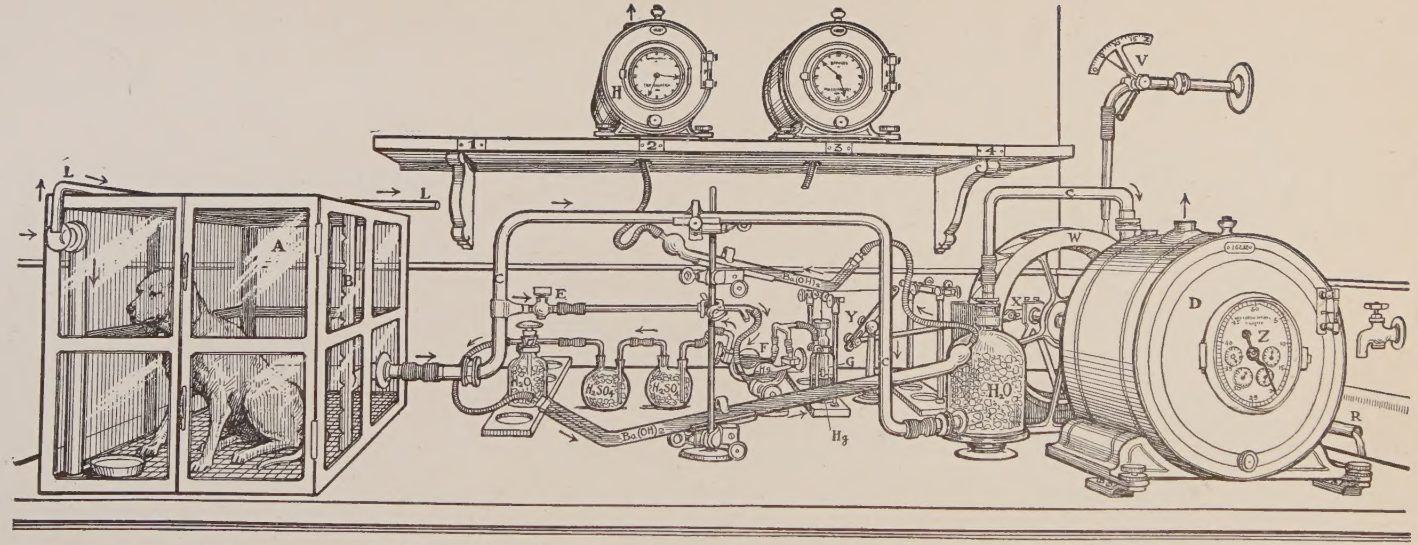

The smaller respiration apparatus of Pettenkofer and Voit. Air enters the cage, A, at the upper left-hand corner. It is drawn out through openings in the tube B (so spaced as to insure thorough diffusion) through the tube, C, and the large H_2O flask, where it is saturated with moisture, to the gas meter, D, where it is measured. The meter is driven by a water wheel, W, rotated at a uniform rate of speed by a constant head of water pressure, V. At E a side tube leads off from C conveying a sample of cage air for analysis. This air is drawn through a mercury valve, F, by means of the mercury pump, G. The latter is operated by the mechanism, X, Y, connected with the water wheel. From the valve F, this air passes through two H_2SO_4 flasks and is then saturated with moisture so as to prevent loss of water from the $Ba(OH)_2$ tubes. Of course, the air, as it leaves the $Ba(OH)_2$ tubes, is saturated with moisture, and is measured by the small gas meter, H, just as in the case of the large meter, while in this saturated condition. A duplicate sample is led off at the same time through another branch of the tube, E, and through another system of vessels to the gas meter at 3. Through the branches of the tube, L, duplicate samples of the air which enters the cage are drawn in the same manner to similar valves, and then through similar vessels and tubes to meters placed at 1 and 4. (Tigerstedt's "Human Physiology.")

THE ELEMENTS

OF THE

SCIENCE of NUTRITION

BY

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Professor of Physiology at the Cornell University Medical College,
New York City

FOURTH EDITION, RESET

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PHILADELPHIA

TO THE MEMORY OF

CARL VON VOIT

MASTER AND FRIEND

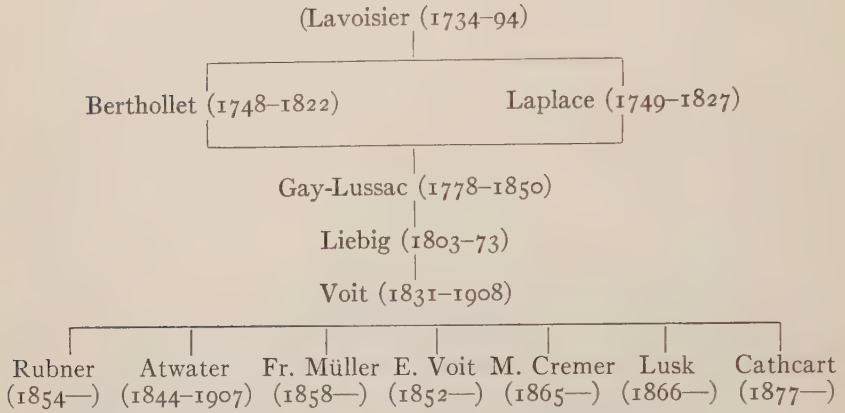
FROM WHOM THE AUTHOR RECEIVED THE INSPIRATION

OF HIS LIFE'S WORK

THIS VOLUME IS DEDICATED

95965

SCIENTIFIC DESCENT OF THE VOIT SCHOOL



Also Gruber, Prausnitz, Straub, Ellinger, Weinland.

Berthollet, coworker of Lavoisier and instructor in chemistry of Napoleon I, bequeathed his sword to Gay-Lussac, his favorite pupil.

Liebig, addressing Humboldt in 1842, said: "The lively interest you took in me procured for me the affection and intimate friendship of my dear teachers, Gay-Lussac, Dulong, and Thénard."

Carl Voit, writing in 1865, said: "The man of science ought to realize the factors which have given him the vantage which he holds. But there are textbooks on physiology and chapters on the animal mechanism which do not even mention the name of Liebig. This anomaly is possible only for those who do not understand history and hold only the new to be worthy of consideration."

Otto Frank writes thus after the death of Voit: "He knew how to get on with men, and was considerate of human weakness. His standards reacted strongly to educate those who surrounded him. He became the leader of a large circle of investigators through whose activity his spirit still lives. . . . The whole life of Carl Voit was dedicated to the advancement of science, to the university he revered and to the common weal."

"The greatest joy of those who are steeped in work and who have succeeded in finding new truths and in understanding the relations of things to each other, lies in work itself."

Carl von Voit.

PREFACE TO THE FOURTH EDITION

In the preparation of the first edition of this book more than twenty years ago the endeavor was made to admit to the introductory chapter only such material as appeared to be susceptible of scientific proof and to make it the key to the rest of the book. In this, the fourth edition, that chapter remains virtually unchanged. The rest of the book shows many important additions to the facts of metabolism and revisions of its theories.

The aim of the book remains the same, to review the scientific substratum upon which rests present-day knowledge of nutrition both in health and in disease. Throughout, no statement has been made without endeavoring to examine the evidence on which it is based.

Laboratory methods to explain the inner processes in disease have been applied to hospital patients for half a century in Germany. In the United States great advances have lately been accomplished in this direction. If such investigations are still further promoted by their discussion here, this writing will not have been in vain.

The author would apologize to all whose claims of priority of discovery have not been duly recognized. The overwhelming mass of the literature makes this a problem of increasing difficulty.

He gratefully acknowledges the helpful criticism of all those who have been his fellow-workers in the laboratory, especially John R. Murlin, E. F. Du Bois, and A. I. Ringer, who for periods of several years were closely associated with him. He would also express his appreciation of the generous support of the experimental work in his laboratory by the authorities of the Cornell University Medical College, as well as by the late Mrs. Russell Sage and the Board of Directors of the Russell Sage Institute of Pathology.

It is, furthermore, a privilege to recognize the great influence which a personal acquaintance with such men as F. G. Benedict and S. R. Benedict, Cathcart, Chittenden, Cremer, Dakin, Folin, Halliburton, A. V. Hill, Hopkins, Kossel, Levene, Magnus-Levy,

Lafayette Mendel, Friedrich von Müller, von Noorden, Rubner, A. E. Taylor, E. Voit, and Zuntz has had upon the conceptions of the subject of nutrition as set down in this book.

He wishes to express his great obligation to a former pupil, Dr. Margaret B. Wilson, who in the first edition painstakingly corrected and improved the manuscript and who through four editions has read the proof. He wishes also to thank Dr. E. F. DuBois for reading the proof sheets. He is indebted to Prof. H. J. Deuel, Jr., for reading the proof and for the preparation of the extensive index. For the careful checking of references and tables he desires gratefully to acknowledge the invaluable services of his secretary, Miss P. R. Schaub.

Finally, the writer desires to apologize for again revising this book in face of the statement that he had no intention to do so. The wishes of his friends compelled him. The hope expressed in the last edition that in another decade the development of scientific knowledge would probably permit the formulation of the subject from the standpoint of physical chemistry has not been fulfilled. It cannot even now be so treated. But the field is open. That the joy of the labor may be as great to him who next reviews the subject as it has been to the writer, is the earnest wish of the author of this the fourth and final edition of this book.

Graham Lusk.

Physiological Laboratory,
Cornell University Medical College,
New York City,
October, 1928

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THE ELEMENTS OF THE SCIENCE OF NUTRITION

CHAPTER I

INTRODUCTORY

Blessed is he who maketh due proofe.
With due proofe and with discreet assaye
Wise men may learn new things every day.
THOMAS NORTON (b. 1493) in Ordinall of Alkimy.

THE earliest scientific observations concerning nutrition were founded upon the commonly noted fact that in spite of the ingestion of large quantities of food, a normal man did not vary greatly in size from year to year. It was understood early in the history of physiology that the weight added by the ingestion of food and drink was lost in the urine, the feces, and the "insensible perspiration." The "insensible perspiration" was partly in evidence when moisture of the warm breath condensed upon a cold plate. By it were meant the usually invisible exhalations from the body, which are now known to be carbon dioxid and water.

Sanctorius[1] made many experiments upon himself and others to determine the amount of insensible perspiration. An old cut shows him sitting in a chair suspended from a large steelyard. As a matter of routine he determined his own weight previous to each meal and then weighted the steelyard so as to counterbalance the additional food he proposed to eat. During the meal when the chair dipped he ended his repast.

In Section I, Aphorism II, Sanctorius gives the following curious advice: "If a physician who has the care of another's health is acquainted only with the sensible supplies and evacuations, and knows nothing of the waste that is daily made by the insensible per-

[1] Sanctorius: "De medicina statica aphorismi," Venice, 1614. Translation by John Quincy, M.D., London, 1712.

spiration, he will only deceive his patient and never cure him." Aphorism III reads: "He only who knows how much and when the body does more or less insensibly perspire will be able to discern when or what is to be added or taken away either for the recovery or preservation of health."

Nicholas Le Fèvre in his Traité' de Chimie (Paris, 1660) noticed the increase in the weight of metals after calcining them and believed this due to the fixation of a gaseous element. He called it *esprit universel*, and applied the same conception to the respiration of animals.

In 1668 John Mayow, writing in London, stated that the atmosphere contained a constituent which supported combustion as well as animal life. (Nitro-aerial particles or fire air particles.)

The modern era of the science of nutrition was opened by Lavoisier in 1780. He was the first to apply the balance and the thermometer to the investigation of the phenomena of life, and he declared "La vie est une fonction chimique." The work of today is but the continuation of that done a century and more ago. Lavoisier and Laplace made experiments on animal heat and respiration. The great German chemist Liebig received his early training in Paris, residing there in 1822. Liebig's conception of the processes of nutrition fired the genius of Voit to the painstaking researches which laid the foundation of his Munich school. These have been repeated and extended by his pupils, of whom Rubner is chief, and by others the world over. Thus the knowledge often transmitted personally from the master to the pupil, to be in turn elaborated, had its seed in the intellect of Lavoisier. It was he who first discovered the true importance of oxygen gas, to which he gave its present name. He declared that life processes were those of oxidation, with the resulting elimination of heat. He believed that oxygen was the cause of the decomposition of a fluid brought to the lungs, and that hydrogen and carbon were produced in this fluid and then united with oxygen to form water and carbon dioxid. He said that perspiration regulated the quantity of heat lost from the body and that digestion replenished the blood with the materials eliminated through respiration and perspiration. It was he who first made respiration experiments on man, the results of which are briefly described in a letter to Black,[1]

[1] Report of the British Association for the Advancement of Science, Edinburgh, 1871, p. 189.

written in Paris and dated November 19, 1790. The more important conclusions Lavoisier sums up as follows:

1. The quantity of oxygen absorbed by a resting man at a temperature of 26° C. is 1200 *pouces de France*[1] hourly.
2. The quantity of oxygen required at a temperature of 12° C. rises to 1400 *pouces*.
3. During the digestion of food the quantity of oxygen amounts to from 1800 to 1900 *pouces*.
4. During exercise 4000 *pouces* and over may be the quantity of oxygen absorbed.

The results may thus be summarized:

RESPIRATION EXPERIMENTS ON MAN

Condition	Environmental Temperature	Oxygen Absorbed per Hour	
	Degrees	Pouces	Liters
(1) Without food	26	1210	24
(2) Without food	12	1344	27
(3) With food	..	1800–1900	38
(4) Work (9195 foot pounds) without food	..	3200	65
(5) Work (9750 foot pounds) with food	..	4600	91

These remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxid excreted depends primarily on (1) food, (2) work, and (3) temperature was established by Lavoisier within a few years after his discovery that oxygen supported combustion. Writing in 1849 Regnault and Reiset say, "Les recherches modernes ont confirmé ces vues profondes de l'illustre savant."

We do not know the exact method employed by Lavoisier by which he obtained these remarkable results. But Nysten[2] investigated the chemistry of respiration in disease by separating the inspired air from the expired air by means of a valve, and collecting the expired air in a bladder. He analyzed this air by shaking it with lime water over mercury in a graduated cylinder and then absorbed the oxygen by phosphorus. This work was contemporary with the development of the percussion of the chest by Auenbrugger and the invention of the stethoscope by Laennec.

[1] 1 cubic pouce = 0.0198 liter.
[2] Nysten: Meckel's Deut. Arch. Physiol., 1817, **3**, 264.

After Lavoisier's work it was quickly noted that if carbon and hydrogen burned in the lungs, the greatest heat would be developed there, a result not in accordance with observation. It was then suggested that the blood dissolved oxygen, and that the production of carbon dioxid and water took place through oxidation within the blood. In 1837 Magnus[1] discovered that the blood did hold large quantities of oxygen and carbon dioxid, which gave apparent support to this theory. Ludwig in his later years believed that the oxidation took place in the blood.[2]

Magendie was the first to differentiate between various forms of food, protein, carbohydrate, and fat and to evaluate them experimentally. Through the critical studies of Liebig, which were published in 1842, it was seen that it was not carbon and hydrogen which burned in the body, but protein, carbohydrates, and fat. Liebig's original theory was that while oxygen caused the combustion of fat and carbohydrates, the breaking down of protein was caused by muscle work. It will be shown later that oxygen is not the cause of the decomposition of materials in the body, but that this decomposition proceeds from unknown causes, and the products involved unite with oxygen. The sum of these chemical changes of materials under the influence of living cells is known as *metabolism*. This process may involve two factors, *catabolism*, or the reduction of higher chemical compounds into lower, and *anabolism*, or the construction of higher substances from lower ones.

Boussingault[3] in 1839 devised a method which was prophetic of future metabolism studies. He analyzed the fodder of a milch cow and determined its content of carbon, hydrogen, nitrogen, and oxygen. He then determined the quantities of the same elements lost by the cow in the urine, feces, and milk. He computed the quantities of these elements lost in the respiration by deducting the second values from the first, as follows:

	C	H	O	N
Elements in the fodder, gm.	4813	595	4035	202
Elements in urine, feces, and milk, gm.	2602	332	2083	175
Balance for respiration, gm.	2211	263	1952	27

Boussingault united 1952 gm. of oxygen with hydrogen to form water and found that there remained unoxidized 19.8 of the 263 gm. He calculated that 19.8 gm. of hydrogen would require 158 gm. (110.6

[1] Magnus: Annalen d. Physik u. Chem. 1837, **40**, 583.
[2] Oral statement to the writer.
[3] Boussingault: Annales de chim. et de physique, 1839, **71**, 113.

liters) of inspired oxygen to convert it into water and that the 2211 gm. of carbon would require 5788 gm. (4051.6 liters) of such oxygen to convert it into carbonic acid. Boussingault concludes that a cow would deprive 19 sq. meters of air of its oxygen content in 24 hours.

"In ordinary alimentation," Boussingault reasons, "an individual does not change his average weight. This state of affairs exists when an animal consumes a *maintenance ration* (ration d'entretien)."

Boussingault notes that one nitrogen balance will not determine whether or not nitrogen as a gas enters into the metabolism of protein.

The validity of Boussingault's method was accepted by Liebig, and he copied the principle of the procedure in the case of experiments on a company of the Grand Ducal Guards of Hesse-Darmstadt.

Liebig was the father of the modern methods of organic analysis, and with him began the great accumulation of knowledge concerning the chemistry of the carbon compounds, including many products of the animal economy. These discoveries gave the world a knowledge of the constitution of foods, of urine, of feces, and of tissues, which was not possessed by Lavoisier.[1]

NITROGEN EQUILIBRIUM

Liebig applied to the problems of biology the mental wealth of the newer chemistry which he himself was creating. He knew that protein contained nitrogen, and in 1842 he suggested that the nitrogen in the urine might be made a measure of the protein destruction in the body.[2] Dumas and Cahours[3] about the same time said that 15 to 16 grams of nitrogen ingested in the diet were recoverable in the 30 to 32 grams of urea in the urine of a day. Bidder and Schmidt[4] were the first to make systematic experiments upon this subject. They gave meat to dogs and cats and found that almost all the nitrogen contained in the meat was eliminated in the urine and in the feces. They[5] make the following striking statement, which rings quite true to

[1] For further historical details consult Lusk: "A History of Metabolism" in "Endocrinology and Metabolism," New York and London, 1922, **3**, p. 3; Krummacher, O.: Ergeb. d. Physiol., 1906, **5**, 746.

[2] Liebig, J.: "Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie," Braunschweig, 1842.

[3] Dumas and Cahours: Compt. rend. acad. sci., 1842, **15**, 976.

[4] Bidder, F., and Schmidt, C.: "Die Verdauungssäfte und der Stoffwechsel," Mitau and Leipzig, 1852, pp. 333, 339.

[5] Bidder, F., and Schmidt, C.: *Ibid.*, p. 387.

modern thought concerning protein metabolism: "Almost all the nitrogen of protein and collagen is split from its combination and carries with it enough carbon, hydrogen, and oxygen to form urea; the remaining part, containing five-sixths of the total heat value of the protein, undergoes oxidation to carbon dioxid and water which are eliminated in the respiration, the calorifacient function having been fulfilled." The results obtained by Bidder and Schmidt were attacked and were not finally established until proof was afforded by Carl v. Voit,[1] who established the fact that an animal could be brought into what he called nitrogenous equilibrium. In this condition the nitrogen of the protein eaten was equal to the nitrogen eliminated from the body in the urine and feces. Thus Voit[2] fed a dog for fifty-eight days with 29 kilograms of meat containing 986 grams of nitrogen, and found 982.8 grams of nitrogen in the excreta of the period. The amount of N in the urine was 943.7 grams, and in the feces 39.1 grams. The difference between the amount of nitrogen ingested and that recovered in the excreta was only $\frac{3}{10}$ of 1 per cent. It therefore seemed extremely probable that the excretory outlet for protein nitrogen was in the urine and in the feces and that other sources of its loss were normally negligible. But in order to establish the fact it was necessary to consider the following questions:

Is the nitrogen of the air built up into organic compounds within the body? Is any protein nitrogen given off as nitrogen gas? As ammonia gas? In the sweat? How much is lost through the growth of the hair, nails, and epidermis?

Lavoisier had said that nitrogen gas had nothing to do with respiration. Regnault and Reiset[3] sometimes found that animals under a bell-jar absorbed nitrogen gas and at other times gave it off. The quantity in both cases was extremely small and can be explained by slight errors in gas analysis due to inexact temperature records. Regnault and Reiset found no measurable quantities of ammonia or of sulphur-containing gases in the expired air, and they discovered that hydrogen might replace nitrogen in the atmosphere without affecting the course of metabolism.

The experiments of Bachl[4] showed that a rabbit with a tracheal cannula could be made to expire for six hours through Nessler's

[1] Voit, C.: "Physiologisch-Chemische Untersuchungen," Augsburg, 1857.
[2] Voit, C.: Z. f. Biol., 1866, **2**, 35.
[3] Regnault, V., and Reiset, J.: An. de chimie et phys., Paris, 1849, Sec. 3, **26**, 299.
[4] Bachl, M.: Z. f. Biol., 1869, **5**, 61.

reagent without the indication of a trace of ammonia in the breath. The lungs are not permeable to ammonia.[1] The most recent statement[2] affirms that when alveolar air contains 5 to 6 per cent. of CO_2 and the blood as little as 0.02 per cent. ammonia none of the latter passes through the alveolar membrane (see p. 263).

The ordinary insensible perspiration is not accompanied by any appreciable loss of nitrogenous excreta, although profuse sweating certainly brings out some urea, uric acid, and other nitrogen extractives normally excreted in the urine. The experiments of Benedict[3] show that the cutaneous excretions of a resting man may amount to 0.071 gram nitrogen *per day;* of a man at moderate work to 0.13 gram *per hour*, and at hard work for four hours to 0.22 gram *per hour*.

From a number of other experiments of similar nature one may quote those of Berry[4] which show that, after accomplishing a quantity of mechanical work upon a stationary bicycle ergometer equal to 142,800 kilogrammeters during four hours, the 2.55 kg. of sweat produced contained 0.56 gm. of nitrogen and 1.67 gm. of sodium chlorid, or respectively 3.7 per cent. and 16.6 per cent. of the total elimination during twenty-four hours of these constituents in the urine and sweat combined.

It may be added that the total nitrogen loss in the menstrual flow of six periods in three women varied between 1.5 gm. and 3.4 gm. per period or 0.31 to 0.84 gm. *per day*.[5]

Voit[6] collected the hair and epidermis from a dog for 565 days and found an average daily output of 1.2 grams with 0.18 gram of nitrogen. Moleschott[7] cut the hair and nails of several men once a month. The daily outgrowth of hair was 0.20 gram with 0.029 gram of nitrogen, and of nail substance 0.005 gram with 0.0007 gram of nitrogen. The waste through the human epidermis has not been measured, but it must be very slight. The above sources of error were thus shown to be negligible.

The view that the nitrogen of the urine and feces could be made a measure for the determination of protein metabolism was thus

[1] Magnus, R.: Arch. exper. Path. u. Pharm., 1902, **48,** 100.
[2] Liljestrand, G., van Wijngaardere, C. de L., and Magnus, R.: Pflüger's Arch gesam. Physiol., 1922, **196,** 247.
[3] Benedict, F. G.: J. Biol. Chem., 1906, **1,** 263.
[4] Berry, E.: Biochem. Z., 1916, **72,** 285.
[5] Gillett, L. H., Wheeler, L., and Yates, A. B.: Am. J. Physiol., 1918–19, **47,** 25.
[6] Voit, C.: Z. f. Biol., 1866, **2,** 207.
[7] Moleschott, J.: Atti della R. Acad. d. Scienze di Torino, 1878, **14.** See also Berthold: Müller's Arch. Anat. Physiol. und wissensch. Med., 1850, p. 156.

securely established. Urea, the principal nitrogenous end-product derived from protein, was therefore shown to be not an adventitious product, but one normally proportional to the protein destruction. It was known that meat protein in general contained about 16 per cent. of nitrogen, or 1 gram of nitrogen in 6.25 grams of protein. Therefore for every gram of nitrogen found in the excreta, 6.25 grams of protein have been destroyed in the body. It is evident that if protein nitrogen be retained in the body a new construction of body tissue is indicated, whereas if more nitrogen is eliminated than is ingested with the food, a waste of body tissue must take place. The discovery of the method of calculating the protein metabolism led Voit to suggest to Pettenkofer that he construct an apparatus with which the total carbon excretion might be measured, including that of the respiration as well as that of the urine and the feces. Voit saw that with these data it would be possible to determine just how much of each food-stuff was actually burned in the human body. He has described the delight which he and Pettenkofer experienced when their wonderful machine began to tell its tale of the life processes. The cost of the apparatus, which was considerable, was defrayed by King Maximilian II of Bavaria.

RESPIRATORY METABOLISM

The form of Lavoisier's apparatus is illustrated in two water-color drawings[1] made by Madame Lavoisier which are now in the possession of his descendants. A face mask made of copper[2] is still among the relics owned by the family. But the method is unknown, for on May 8, 1794, Lavoisier was executed by the Paris Commune before he was able to publish his results in full (see p. 19).

In 1850 Regnault and Reiset[3] published an account of respiration experiments in which small animals were placed under a bell-jar containing a known quantity of oxygen. The air was kept free from carbon dioxid by pumping it through potassium hydrate, and oxygen was added from time to time. The gaseous exchange between the animal and its environment could be readily ascertained by determining the amount of carbon dioxid given off and the amount of oxygen absorbed. No attempt was made to determine from what materials the carbonic acid arose. The method of Regnault and

[1] Grimaux, E.: Lavoisier, Paris, 1888.
[2] Lusk, G.: J. Am. Med. Assn., 1925, **85**, 1246.
[3] Regnault, V., and Reiset, J.: An. d. Chim. und Pharm., 1850, **73**, 92, 129, 257.

Reiset placed the animals in a confined space where excreta other than carbon dioxid could collect, and where the atmosphere became saturated with water. However, these factors were without influence on the health of their animals. They planned to work in one of the large hospitals in Paris, but, unfortunately, the project proved too costly and had to be renounced. They write, "L'étude de la respiration de l'homme dans ses divers états pathologiques nous paraît un des sujets les plus dignes d'occuper les hommes qui se vouent à l'art de guérir: elle peut donner un diagnostic précieux pour un grand nombre de maladies et rendre plus évidentes les revolutions qui surviennent dans l'économie." Although Regnault and Reiset had no exact idea of the quantity of the materials which were oxidized in the animals with which they were experimenting (see p. 62), we find that Bischoff and Voit[1] tried to read such interpretations into the work of Regnault and Reiset. Thus Bischoff and Voit determined the quantity of nitrogen in the urine of a starving dog, which indicated that he had burned in twenty-four hours 218 grams of his own "flesh." The flesh was calculated from the nitrogen elimination on the basis of the assumption that fresh meat contains 3.4 per cent. of nitrogen. Many of the older experiments were computed on this basis. It was shown that the 218 grams of "flesh" contained 40 grams of carbon. Bischoff and Voit estimate from the experiments of Regnault and Reiset that a meat-fed dog of a weight similar to the above would give off 250 grams of carbon and absorb 900 grams of oxygen in the respiration of twenty-four hours. These figures indicated to Bischoff and Voit that the extra carbon elimination was due to the combustion of fat, and they reached the conclusion that the waste of the body in starvation is dependent on the metabolism of protein and fat. Correct results, however, were attainable only by combining the two methods, so that both the quantity of the nitrogen and carbon of the urine and feces and the amount of carbon dioxid of the respiration during the same period of time could be ascertained. This was accomplished by the respiration apparatus of Pettenkofer.

The problem to be solved by Pettenkofer included the maintenance of a man in normal surroundings. A small room was therefore constructed which was well ventilated by a current of air. This air

[1] Bischoff, T. L. W., and Voit, C.: "Die Gesetze der Ernährung des Fleischfressers," Leipzig and Heidelberg, 1860, p. 43.

entered the chamber freely through an opening in connection with a large room outside and was aspirated from a second opening in the chamber, through a large gas-meter, where its volume was measured (500,000 liters per day). It was evidently impracticable to determine all the carbon dioxid in this large volume of air, but its amount was calculated from the analysis of duplicate samples continually withdrawn from the air leaving the chamber during the time of the experiment. Each sample, as it was pumped out, was made to pass over calcined pumice stone soaked in sulphuric acid, to remove the water. Next it bubbled through baryta water to remove the carbon dioxid, and then passed through a small gas-meter, where the volume of the sample was measured. After this fashion the amount of carbon dioxid and water coming from the air of the chamber was determined in duplicate. Other duplicate analyses of the air taken outside the ventilator just before it entered the chamber were simultaneously made in the same manner as were the analyses of the chamber air itself. Knowing the quantity of carbon dioxid and water entering and leaving the room, it was easy to calculate how much was derived from the man living in it during the period of experimentation. The experimenters failed to find any other gaseous exhalation from a man, such as ammonia, hydrogen, or methane, which could vitiate their results. Control experiments were made by burning a candle or evaporating a known weight of water within the room. Analysis showed that the carbon dioxid and water so produced were measurable within 1 per cent. of error.

As an illustration of the practical working of the respiration apparatus the first experiment of Pettenkofer and Voit,[1] which gives the metabolism in a starving man, will be described. The man was allowed a small quantity of Liebig's extract of beef, as the experimenters did not at that time realize the very slight discomfort usually entailed by total abstinence from food. As Liebig's extract has no nutritive value, its effect has been counted out in the following description. The reader should note that the large decimal figures cited below portray an impossible degree of accuracy.

The subject, on entering the living-room of the apparatus, weighed 71.090 kilograms, and he drank during the day 1.0548 liters of water, making a total body weight of 72.1448 kilograms. Twenty-four hours later he weighed 70.160 kilograms and his excreta had

[1] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1866, **2**, 478.

amounted to 0.7383 kilogram carbon dioxid, 0.8289 kilogram water from lungs and skin, and 1.1975 kilograms of urine. The final body weight plus all the excreta amounted to 72.9247 kilograms. A total body weight of 72.1448 kilograms was converted into a body weight plus excreta amounting to 72.9247 kilograms. The difference is due to oxygen absorbed. The difference of 0.7799 kilogram represents the amount of oxygen needed to convert the body substance lost into the excretory products obtained. The tabular statement reads:

MAN—STARVATION

	Kg.		Kg.
Weight at start	71.090	Weight at end	70.160
Water drunk	1.0548	Carbon dioxid	0.7383
		Water in respiration	0.8289
Oxygen absorbed	0.7799	Urine	1.1975
	72.9247		72.9247

The analysis of the urine showed 12.51 grams of nitrogen and 8.25 grams of carbon. A calculation gives the amount of carbon in the respiration as 201.3 grams. If we neglect the feces as being too small in starvation to influence the results, we find that the total carbon elimination for twenty-four hours was 209.55 grams, and the total nitrogen 12.51. In the Liebig extract ingested there were 2.44 grams of carbon and 1.18 grams of nitrogen, which must be deducted from the above in order to obtain the strict loss of carbon and nitrogen from the body during the period of starvation. These values are:

C	207.11 grams.
N	11.33 "

These two figures enabled Pettenkofer and Voit to calculate what substances had burned in the body. As every gram of nitrogen in the excreta is approximately represented by the destruction of 6.25 grams of meat protein, the amount of such protein destroyed by the man was 70.81 grams. It has been found that for every gram of nitrogen present in meat protein there are 3.28 grams of carbon. It is therefore easy to estimate that destruction of protein represented by 11.33 grams of nitrogen involved the elimination of 37.16 grams of carbon. Now, the man eliminated 207.11 grams of total carbon, from which this protein carbon may be deducted, leaving as residue 169.95 grams, which must have originated from a source other than

protein. The possible sources are two in number—carbohydrates and fats. In starvation no carbohydrates are ingested and their supply in the form of reserve glycogen is usually counted as being negligible in such experiments as these. The only other source from which the 169.95 grams of extra carbon could have been derived is fat, and as fat contains 76.52 per cent. of carbon, a destruction of 222.1 grams of fat may be calculated. This fasting man therefore destroyed:

Protein	70.81 grams.
Fat	222.1 "

That such metabolism actually did take place was further indicated by the comparison of the amount of oxygen needed for the destruction of the above constituents, and the amount of oxygen absorption as determined by the experiment.

From the constituents of the protein and fat destroyed, Pettenkofer and Voit deducted the constituents of the urine, which contains part of the C and H belonging to protein. The balance of the carbon and hydrogen was fit for oxidation to carbon dioxid and water. Their calculation may thus be presented:

	Weight in Grams		
	C	H	O
Composition of the protein burned	37.16	5.8	17.1
Composition of fat burned	169.95	25.7	25.1
Total C, H, and O metabolized	207.11	31.5	42.2
Deduct quantity in the urine	8.2	2.0	7.6
Balance available for respiratory CO_2 and H_2O	198.9	29.5	34.6
Oxygen required	530.4	235.7	

Total O required for the formation of CO_2 and H_2O	766.1
Less O in the protein and fat	34.6
Oxygen actually required	731.5
Oxygen absorption as determined	779.9
Difference	48.4

We may reach the same result by using the most modern figures for the oxygen requirement in the metabolism of the food-stuffs. We now know that to burn 100 grams of meat protein requires 133.43 grams of oxygen, and to burn 100 grams of fat requires 288.5 grams,

and to burn 100 grams of starch 118.5 grams. This being true, there are required:

	Oxygen
For 70.81 grams protein	94.44 gm.
For 222.1 grams fat	639.55 gm.
Total required	733.99 gm.
Oxygen absorption as found	779.9 gm.
Difference	45.91 gm.

Had carbohydrates burned, less oxygen would have been needed, since carbohydrates contain a larger proportion of oxygen than fats. Had the extra 169.95 grams of carbon been due to the combustion of starch (or glycogen), 382 grams would have burned, requiring 452.7 grams of oxygen instead of 639.5 grams for fat. Pettenkofer and Voit found in the amount of oxygen absorption a confirmation of their belief that the fasting organism supports itself by the combustion of its own protein and fat.

It is apparent from this discussion that *the quantity of oxygen needed in metabolism depends upon the chemical composition of the material that burns in the organism*, and also that the relation between the amount of oxygen absorbed and carbon dioxid excreted depends on the same factor. Regnault and Reiset frequently observed that this latter relationship was variable. The ratio of the *volume* of carbon dioxid expired to the *volume* of oxygen inspired during the same time is called the *respiratory quotient* (see p. 62). When carbohydrates burn, the R. Q. is unity; that is, for every hundred volumes of carbon dioxid excreted a hundred volumes of oxygen are absorbed. When protein burns the quotient is $\frac{\text{Vol. } CO_2}{\text{Vol. } O_2} = \frac{78.1}{100}$ or 0.781, and when fat burns the quotient is 0.71. Pettenkofer and Voit calculated that the respiratory quotient in their fasting man was 0.69. This indicated a combustion of fat in the organism.

The further researches of Pettenkofer and Voit were founded on the principles described in the above experiment on a fasting man. If meat and fat were ingested, the carbon and nitrogen excreta were collected, and from these data it was determined how much of each food-stuff was oxidized and whether there was a storage of either in the body or a loss of either from the body. If a mixed diet which included carbohydrates were given, the carbon dioxid elimination increased and the oxygen absorption was such as indicated the

combustion of carbohydrates. It was assumed that after deducting the protein carbon from the total carbon eliminated, the balance of extra carbon was derived from the destruction of the carbohydrates in so far as these were ingested; any carbon in excess of this was attributed to fat combustion.

FUNDAMENTAL CONCLUSIONS

Voit,[1] in his necrology of Pettenkofer, writes: "Imagine our sensations as the picture of the remarkable processes of the metabolism unrolled before our eyes, and a mass of new facts became known to us! We found that in starvation protein and fat alone were burned, that during work more fat was burned, and that less fat was consumed during rest, especially during sleep; that the carnivorous dog could maintain himself on an exclusive protein diet, and if to such a protein diet fat were added, the fat was almost entirely deposited in the body; that carbohydrates, on the contrary, were burned no matter how much was given, and that they, like the fat of the food, protected the body from fat loss, although more carbohydrates than fat had to be given to effect this purpose; that the metabolism in the body was not proportional to the combustibility of the substances outside the body, but that protein, which burns with difficulty outside, metabolizes with the greatest ease, then carbohydrates, while fat, which readily burns outside, is the most difficultly combustible in the organism."

Since the days of these researches repeated experiments have established the verity of the conclusions drawn. It is interesting to note that among the earliest experiments made were some upon patients in pathologic conditions, one suffering from leucemia, another from diabetes.

Besides the influence of foods upon metabolism, the changes brought about by exercise, temperature, and drugs were investigated not only by the Munich school, but by many other workers. Similar investigations are actively progressing to-day.

Among the important conclusions reached by Voit was that concerning the manner of the metabolism. It has been stated that Liebig believed that fat and carbohydrates were destroyed by oxygen, while protein metabolism took place on account of muscle work.

[1] Voit, C.: Z. f. Biol., 1901, **41**, 1.

Voit[1] *showed that muscle work did not increase protein metabolism and that the metabolism was not proportional to the oxygen supply.* The oxygen absorption apparently depended upon what metabolized in the cells. Voit believed that the cause of metabolism was unknown, that the process was one of cleavage of the food molecules into simpler products, which could then unite with oxygen. Yeast cells, for example, convert sugar into carbonic acid and alcohol without the intervention of oxygen. In like manner the first products of the decomposition of fat, sugar, and protein are formed in metabolism through unknown causes. Some of these preliminary decomposition substances may unite with oxygen to form carbon dioxid and water, others may be converted into urea, while others under given circumstances may be synthesized to higher compounds. In any case *the absorption of oxygen does not cause metabolism, but rather the amount of the metabolism determines the amount of oxygen to be absorbed* (see p. 32).

The statement is frequently met with in the literature of the subject that such and such a disease is the consequence of deficient oxidative power in the tissues. For example, it has been stated that alcohol decreases the oxidative power of the liver for uric acid.[2] Such apparent decrease in oxidative power may, however, be due to the fact that the normal oxidizable cleavage products are not formed and, therefore, no oxidation can take place. It is not due to lack of oxygen that sugar is not oxidized in diabetes, or cystin in cystinuria. There is the normal supply of oxygen present, but the cleavage of these substances into bodies which can unite with oxygen cannot be effected, and hence they cannot be metabolized.

One must remember that in alcoholic fermentation with yeast sugar is broken into about equal weights of carbon dioxid and alcohol, and there is no oxidation no matter how much oxygen is available.

Voit's pupil, Lossen,[3] stated that the carbon dioxid elimination in respiration was independent of the ventilation of the lungs except in so far as forced breathing increased the muscular work and the consequent output of carbon dioxid. (See discussion on p. 96.)

[1] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1866, **2**, 535.
[2] Beebe, S. P.: Am. J. Physiol., 1904, **12**, 36.
[3] Lossen, H.: Z. f. Biol., 1866, **2**, 244; 1870, **6**, 298.

When the depth of respiration was *voluntary* the results were as follows:

Number of Respirations per Minute	Volume of Expired Air in 15 Minutes	Volume of One Respiration	CO_2 in 15 Minutes
	Liters	C.C.	Grams
5	75.1	1002	7.96
10	83.6	558	7.44
15	94.4	420	7.32
20	120.3	401	8.14
30	121.0	269	7.18
40	138.5	231	6.76
60	182.7	203	6.63

Pflüger,[1] who through different reasoning came to the same conclusion as Voit, devised an experiment in which a rabbit breathed quietly through a cannula, and the oxygen absorption was compared with that of the same animal when rapid artificial ventilation of the lungs with air took place, producing apnea or hyperarterialization of the blood. There was no difference, as is seen from the following table:

	Oxygen Absorbed in C.C. during 15 Minutes	
	Normal Respiration	Apnea
Series I	201.66	203.88
Series II	203.21	210.47

From these experiments it is made sure that the respiration does not cause or regulate metabolism. On the contrary, the metabolism regulates the respiration. *The metabolism of the tissues, through its oxygen requirement and its carbon dioxid production, changes the condition of the blood and thereby regulates the respiration. These distinctions are of fundamental importance.*

Thus far the history of the principles which underlie the exact measurement of the metabolism has been briefly given. By metabolism is meant the chemical changes of materials under the influence of living cells. The first cause of these chemical changes, it has been seen, is unknown, but their results lead to motions of the smallest component parts of protoplasm, motions whose totality we call life. Phenomena of life are phenomena of motion due to liberation of

[1] Pflüger, E.: Pflüger's Arch. ges. Physiol., 1877, 14, 1.

energy in the breaking down of molecules. The motions are principally manifested as heat, mechanical energy, and electric currents. In the organism mechanical energy may be converted into heat, as appears when work of the heart is converted into heat by the friction of the blood upon the capillaries. Also the current of electricity developed at each systole of the heart, or in any other active tissue, is resolved into heat. Thus heat may become a measure of the total activity of the body. It is derived from the total metabolism and must be dependent on it and be a measure of it. Hence the physical activities noted in life are the results of chemical decompositions. Metabolism vivifies the energy potential in chemical compounds.

THE BIRTH OF ANIMAL CALORIMETRY

Lavoisier[1] was the first to recognize that animal heat was derived from the oxidation of the body's substance and he compared animal heat to that produced by a candle. To prove this he burned a known quantity of carbon in an ice-chamber and noted the amount of ice melted. He then calculated the amount of heat produced from a unit of carbon. He and Laplace put a guinea-pig in an ice-chamber and noted the amount of ice which melted during ten hours and calculated the heat given off from the animal.[2] They then determined how much carbon dioxid the guinea-pig gave off. The animal yielded 31.82 calories to the ice-chamber, while a calculation from the respiratory analysis showed that 25.408 calories could have been derived by the burning of enough carbon to yield the same amount of carbon dioxid as was eliminated by the animal.

Lavoisier realized several of the errors in his work. For example, the calorimetric determination on the animal was made at a different temperature from that of the respiratory experiment, and Lavoisier knew that cold would raise the carbon dioxid output. Also cold reduced the heat in the animal itself, and, further, the water of respiration was added to that of the melting ice. But Lavoisier concluded that the source of the heat lay in the oxidation of the body.

Later in 1785 after the discovery of hydrogen by Cavendish, Lavoisier stated that when oxygen is absorbed it is used in part to oxidize carbon and the rest to oxidize hydrogen in the lungs, and in

[1] Lavoisier, A. L., and Laplace, P. S.: Mém. Acad. d. Sci., 1780, p. 379.

[2] This calorimeter and other important apparatus of Lavoisier are exhibited at the Conservatoire des Arts et Métiers at Paris.

this manner he believed the discrepancy between the heat calculated and the heat found in the guinea-pig could be explained.

Crawford, in England in 1777, found after burning wax and carbon, or on leaving a live guinea-pig in his water calorimeter, that for every 100 ounces of oxygen used the water was raised the following number of degrees Fahrenheit:

Wax	2.1
Carbon	1.93
Guinea-pig	1.73

Crawford concluded that the heat above produced was due to the transformation of pure air into fixed air (carbon dioxid) and water.

The methods of Crawford, though primitive, were based on fundamental principles, for according to the modern computation of Zuntz the values of heat production where 1 liter of oxygen is used to burn the different food-stuffs in the body are very nearly identical (see p. 68).

In 1823 the French Academy awarded a prize for the best essay on the subject of animal heat. Despretz and Dulong competed for the prize and it was awarded to the former.

Despretz[1] calculated the amount of heat which would have been liberated in burning the carbon and hydrogen of the metabolism to carbon dioxid and water, and compared this with the amount of heat given off by the animal. The heat as calculated was only 74 to 90 per cent. of what was found, a discrepancy in part attributable to a low caloric value used for hydrogen (see p. 68). Had Despretz used the value for 1 gram of hydrogen of 34.46 calories found by Favre and Silbermann in 1852 instead of 23.64 calories which he employed, his calculated heat would have been 98.2 per cent. of the heat eliminated by three guinea pigs in one of his experiments. The modern calculation would be:

O_2 Liters	CO_2 Liters	R.Q.	Calories Indirect	Calories Direct
3.30	2.59	0.78	15.86	14.68

or 8 per cent. too much calculated heat instead of 11 per cent. too little as determined by Despretz. However, Despretz concluded that although the respiration was the principal source of animal heat, food, the motion of the blood, and friction yielded the remainder.

[1] Despretz: J. de Physiol., 1824, **4**, 143.

Interpretation along the lines of the law of the conservation of energy was obviously beyond the ideas of the time.

Dulong's[1] experiments also led to the same conclusion, that oxidation was insufficient to explain the cause of animal heat, and that there must be other sources of it.

Regnault and Reiset, writing in 1849 regarding the computation of heat production from the oxygen absorbed by an animal, remark, "The phenomena are evidently so complex that it is scarcely probable that one will ever be able to submit them to calculation."

About 1842 James P. Joule supplied the chief experimental data which established the mechanical equivalent of heat. In 1845 J. R. Mayer laid down the law of the conservation of energy, and in 1847 Helmholtz independently made the same discovery. Both contributions were rejected by the leading German scientific journal of the day.[2] This should encourage all workers to rest assured of the ultimate recognition of work that is worth while.

Energy cannot arise from nothing, nor can energy disappear into nothing. Where energy is active it must have been elsewhere potential. The sum total of energy remains constant in the universe, but energy may vary in kind. The kinds include mechanical energy, heat, electricity, magnetism, and potential energy. The source of energy on the earth is the sun, excepting the energy of the tides, which is due principally to the moon. The sun unevenly warms the atmosphere, producing winds which drive ships and windmills. The sun's heat lifts the vapor of water into the atmosphere, producing rain, in consequence of which rivers are made to turn machinery. The sunlight acts upon a mixture of hydrogen and chlorin gas, causing them to unite with a loud explosion, and the sun acts upon the green leaf of the plant, causing it to unite carbon dioxid and water, with the production of formic aldehyd, which is built up into sugar, oxygen being given off in the process. The sun's energy required to build up the compound becomes latent or potential in it. Whenever and wherever this sugar is again converted into carbon dioxid and water by oxidation, exactly the same quantity of energy taken from the sun and made potential in the sugar is set free. This sugar in the plant may be further converted into starch, cellulose, fat, and possibly into protein. Plants furnish wood and coal as fuel for the

[1] Dulong: J. de Physiol., 1823, **3**, 45.
[2] Exner, S.: Wiener klin. Wchnschr., 1914, **27**, 1529.

steam-engine. They also furnish the basis of animal food, yielding substances which can build up animal tissues, and which can furnish the energy necessary to maintain those motions in the cells whose aggregate is called life. These motions appear in the body as heat, mechanical work, and electric currents, all of which may be measured as heat. Is this energy completely derived from the metabolism? This question is but the continuation of the old one of Lavoisier in the light of newer science.

Bischoff and Voit[1] in 1860 still calculated the heat value of the metabolism from the heat developed in burning the carbon and hydrogen elements of the metabolism. They recognized, as had Bidder and Schmidt[2] before them, that this was a false method, and stated that they should employ the calorific value of fat, starch, and protein, less the urea, since they recognized that urea was capable of undergoing combustion with liberation of heat.

In 1860 Voit[3] took a Thomson calorimeter with him from London to Munich. After Frankland's determination of the heat value of the various food-stuffs and urea Voit[4] prepared a table in 1866 for use in his lectures showing that the metabolism of the fasting man experimented on by Pettenkofer and Voit indicated the production of 2.25 million small calories, while the metabolism on a medium diet was 2.40 million calories.

In 1873 Pettenkofer and Voit[5] calculated that 100 grams of fat were the physiologic equivalent of 175 grams of starch. Liebig at that time had suggested that the amount of these substances which could be burned by a man was proportional to the oxygen supply.

Voit, not content with his results, suggested to Schürmann in 1878–79 that he carry on experiments to see in what way carbohydrates and fat were interchangeable in nutrition. Schürmann died before the work was completed and the investigation was continued by Rubner. *The isodynamic law, which showed that the food-stuffs may under given conditions replace each other in accordance with their heat-producing value, was the result.*

Rubner gives the following as the quantities of the different food-stuffs which are *isodynamic:*

[1] Bischoff, T. L. W., and Voit, C.: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.
[2] Bidder, F., and Schmidt, C.: "Verdauungssäfte und Stoffwechsel," 1852, p. 353.
[3] Voit, C.: Münchener med. Wchnschr., 1902, **49**, 233.
[4] Voit, C.: *Ibid.*
[5] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1873, **9**, 534.

100 gm. fat.
232 gm. starch.
234 gm. cane-sugar.
243 gm. dried meat.

After Stohmann[1] published his research on the calorific value of foods, urea, etc., Voit commenced the construction of a calorimeter for the measurement of the heat eliminated from the body of a man whose metabolism was simultaneously determined. The results obtained by the use of this machine were never published.

Rubner[2] in Voit's laboratory during this same period was making a series of valuable calorimetric determinations. The heat value to the body of burning starch and fat were obviously the same as that determined in the calorimeter, since in both cases the same end-products, carbon dioxid and water, resulted. The heat value of protein in the calorimeter was different from its fuel value to the body, since the end-products were different in the two cases. When protein is oxidized in the body the products of its metabolism are lost in three different ways—through the respiration, urine, and feces. The last two contain latent heat lost to the body, which must be deducted from the heat value of protein determined calorimetrically.

The custom of Stohmann and previous authorities had been to deduct the heat value of urea from the heat value of protein in order to obtain the actual physiologic or fuel value of protein for the organism. But in the earliest experiments of Pettenkofer and Voit[3] it was recognized that in starvation and after the ingestion of meat there was a much larger output of carbon in the urine than corresponded to the quantity of urea present. The ratio of nitrogen to carbon was nearly constant in the urine when the nutritive conditions were similar. If urea alone were present, Rubner estimated there would be 0.429 gram of C to 1 of N or N:C = 1:0.429. In starvation the urine contains extractive nitrogen (creatinin, uric acid, etc., having relatively more carbon than urea) which has been derived from the breaking down of tissue protein, and the ratio is N:C = 1:0.728. When meat was ingested the fact that the food contained these extractives made the C:N ratio 0.610. And even after six days' ingestion of meat washed free from extractives the urine of the seventh and eighth days still showed an elimination of

[1] Stohmann, F.: J. prak. Chem., 1885, **31**, 273, and earlier papers.
[2] Rubner, M.: Z. f. Biol., 1885, **21**, 250, 337.
[3] Pettenkofer, M., and Voit, C.: *Ibid.*, 1866, **2**, 471.

carbon other than that due to urea, as was indicated by the ratio 0.532. Therefore, from the metabolism following the ingestion of the proteins of washed meat small amounts of carbon compounds other than urea are eliminated in the urine.

Rubner saw that it was the heat value of the urinary constituents themselves which had to be subtracted from the heat value of protein if the fuel value of protein to the body was to be determined.

The following table shows Rubner's results after burning the dry urine:

CALORIFIC VALUE OF URINE

Material Burned	C:N	Calories from 1 Gram	Calorific Value of 1 Gram N
Urea	0.429	2.523	5.41
Urine after feeding protein	0.532	2.706	5.69
Urine after feeding meat	0.610	2.954	7.46
Urine in starvation	0.728	3.101	8.49

Benedict and Milner[1] report that the average C:N ratio in man when he partakes of a mixed diet is 0.75 and the calorific value of a gram of urinary nitrogen is 8.09. When a diet which is high in carbohydrate is ingested the value of a gram of urinary nitrogen may be from 11 to 13 calories,[2] an increase which is due to the appearance of products of the intermediary metabolism of glucose (see p. 251), and of glucose itself.[3]

It was not alone necessary to know the heat value of the urine excreted, but also that of the feces. Rubner found that after giving 100 parts of dry muscle containing 5.5 grams of ash there was an elimination of 38.2 grams of the organic part in the urine and 2.746 grams in the feces. The following table represents this division of material in the excreta:

	C	H	N	O
Composition of 100 parts dry muscle	50.5	7.6	15.4	20.97
Urine contains 38.2 parts	9.63	2.52	15.16	10.9
Feces contain 2.746 parts	1.67	0.25	0.24	0.54
Excreted in urine and feces	11.30	2.77	15.40	11.44
Balance for respiration	39.2	4.83		9.53

Rubner determined the amount of heat produced from 1 gram of ash-free feces after meat ingestion and found it to be 6.127 calories, while 1 gram of ash-free feces after protein (washed meat) ingestion

[1] Benedict, F. G., and Milner, R. D.: U. S. Dept. of Agriculture, Office of Experiment Stations, 1907, Bull. 175, p. 144.

[2] Tangl, F.: Arch. f. Physiol., 1899, Suppl., p. 251.

[3] Benedict, S. R., Osterberg, E., and Neuwirth, I.: J. Biol. Chem., 1918, **34**, 217.

yielded 6.852 calories. The total calorific value of 1 gram of beef muscle when Rubner burned it in the calorimeter was 5.345 calories. He had now the principal data required to determine its heat value in the body. If from 100 grams of meat 2.746 grams appear as feces having a calorific value of 6.127 calories per gram, then there is here a loss of $6.127 \times 2.746 = 16.83$ calories. If from every 100 grams of meat containing 15.4 grams of nitrogen 15.16 grams of the latter appear in the urine and such urine produced by ingesting meat has a calorific value of 7.46 calories for every gram of nitrogen present, then the energy loss in the urine would be $7.46 \times 15.16 = 112.94$ calories. For dry muscle substance we find therefore:

			Calories
100 grams muscle			534.5
Waste	Urine	112.94	
	Feces	16.83	Total 129.77
Fuel value of 100 grams of dry muscle			404.73

From this value there must be a slight deduction for the heat present in the protein in its colloidal state but lost on drying, and for the heat of solution necessary to dissolve urea and other urinary constituents. Rubner estimates these as:

Heat for the imbibition of protein	2.688
Heat for solution of urea	1.989
	4.677

Subtracting 4.67 from 404.73 leaves 400.06 calories as the maximum of energy obtainable from 100 grams of the dried solids of meat. The calorimeter shows a heat value of 534.5 calories for the same protein. *Of this, 400.06 calories, or 74.9 per cent., are available in the organism, while the remainder, or 25 per cent., goes to waste in urine and feces.*

A further calculation shows that every gram of nitrogen in the urine and feces represents an elimination of heat from protein metabolism equal to 25.98 calories. The heat value of protein under the different physiologic conditions was estimated by Rubner after the above fashion, and may thus be tabulated:

CALORIFIC VALUE OF PROTEIN IN NUTRITION

	Calories Yielded by Metabolism of 100 Grams of Protein in the Body	Heat Value in Calories of Protein Metabolism Yielding 1 Gm. of N in the Excreta
After protein (washed meat) ingestion	442.4	26.66
After meat ingestion	400.05	25.98
Starvation	384.2	24.98

If we know the amount of nitrogen in the excreta we can calculate from these standard figures of Rubner the heat value of the protein metabolism to the body. Rubner found that the heat value of 1 gram of pig's fat (lard) was 9.423 calories. Since fat contains 76.5 per cent. of carbon, it could be calculated that for every gram of carbon eliminated in the respiration, which was the result of fat metabolism, 12.3 calories must have been liberated in the body. These figures enabled Rubner to calculate the amount of heat liberated by the fasting man of Pettenkofer and Voit, whose metabolism we have already discussed. The N excreted was multiplied by 24.98 and the fat carbon by 12.3 which gave the total heat value of the period:

Heat from protein (11.33 Gm. N × 24.98)	283 Cal.
Heat from fat (169.95 C × 12.3)	2091 Cal.
Total heat value of the metabolism as calculated	2374 Cal.

Rubner applied such calculations as these to the material at hand in the literature of the time, and discovered that *the heat value of the metabolism of the resting individual is proportional to the area of the surface of his body.* For example, a man in starvation, or on a medium diet, an infant at the breast, and a starving dog were shown to give off similar quantities of heat per square meter of surface. To these Rubner subsequently added the results of his researches upon a dwarf. The following tables illustrate this point:

	Yield of Calories per Sq. M. Surface in 24 Hours
Adult man in starvation	1134
Dog in starvation	1112
Adult man on a medium mixed diet	1189
Breast-fed infant	1221
Dwarf (weight = 6.6 Kg.) medium mixed diet	1231

This law, that an animal in starvation or on a medium diet and at an environmental temperature of 18° gives off the same quantity of heat per square meter of surface, can be extended so that it applies to all warm-blooded animals. Thus E. Voit[1] has collected data for the following table:

	Weight in Kg.	Calories Per Kilo	Calories Per Sq. M. Surface
Pig	128.0	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Goose	3.5	66.7	967
Fowl	2.0	71.0	947
Mouse	0.018	654.0	1188

[1] Voit, E.: Z. f. Biol., 1901, **41**, 120.

Recent work has confirmed the validity of this "law of surface area," but has somewhat modified the idea of the conditions under which it finds expression (see Chapter V). The figures given above are often only roughly similar to those obtained in modern work.

Rubner from his work on protein considered that the heat value of 1 gram in an average mixed diet might well be placed at 4.1 calories. Of course, such a mixed diet would contain casein (4.4 cal.), the ash-free organic substance of meat (4.233 cal.), and vegetable proteins (3.96 cal.). The daily food allowance for animal protein was put at 60 per cent., for vegetable protein at 40 per cent., of the total protein in the mixed dietary. For the value of neutral fats Stohmann's figures for olive oil, fat of animal tissue, and butter fat were averaged as follows:

Olive oil	9.384	Calories per Gm.
Animal tissue fat	9.372	" "
Butter fat	9.179	" "
Average	9.312	" "

For the heat value of 1 gram of fat in a mixed diet Rubner therefore adopted the value 9.3.

The following heat values have been found for carbohydrates:

	Stohmann	Rubner
Glucose	3.692	3.755
Lactose	3.877	
Sucrose	3.959	4.001
Starch	4.116	

The variations in heat value are principally due to variations in the water content of the different molecules. Considering the predominating importance of starch in the average diet, Rubner gave the value of 4.1 to the group of carbohydrates in the foods.

Rubner's "standard values" have been widely used throughout the world in determining the average fuel value of a mixed diet. They are:

1 gram of protein	4.1	Calories.
1 gram of fat	9.3	"
1 gram of carbohydrate	4.1	"

Their accuracy has been verified by Rubner[1] in the most careful manner.

Rubner states that in these calculations there is no allowance made for incomplete absorption of food materials from the intestine. These differences are too variable to establish a true factor for correction, but usually with mixed diets containing vege-

[1] Rubner, M.: Z. f. Biol., Festschrift zu Voit, 1901, 42, 261.

tables 8 per cent. of the calories of the ingesta are lost in the feces, while with diets rich in fats the loss is only 4.3 per cent. (see p. 53).

Rubner,[1] still working in the Munich laboratory, showed that if the diet were increased from a medium to an abundant amount, the metabolism as indicated by the heat production rose. This *dynamic action* resulting from the excessive ingestion of a food-stuff was greatest with protein.

Finally Rubner, in his own laboratory at Marburg, evolved an animal calorimeter which could accurately measure the amount of heat a dog produced in twenty-four hours. The dog was placed within the chamber of the calorimeter, and this chamber was attached to a respiration apparatus, so that the metabolism could be calculated according to the method of Pettenkofer and Voit. From the metabolism the heat production could be estimated. The results were a triumphant demonstration of the truth of the law of the conservation of energy. The amount of heat calculated by Rubner[2] as the quantity that should have been derived from the metabolism of the dog during the day spent in the calorimeter was the amount actually given off by the dog to the calorimeter. The metabolism, the cause of the motions of life, was the source of the heat-loss of the body. The results achieved constitute a final verification of the methods of calculating the total metabolism originated by Pettenkofer and Voit.

An epitome of Rubner's experiments is here presented:

COMPARISON OF ESTIMATED HEAT FROM METABOLISM WITH HEAT ACTUALLY PRODUCED IN CALORIES

Food	Number of Days	Heat Calculated from Metabolism	Heat Directly Determined	Difference in Percentage
Starvation	5	1296.3	1305.2	−1.42
	2	1091.2	1056.6	
Fat	5	1510.1	1498.3	−0.97
Meat and fat	8	2492.4	2488.0	
	12	3985.4	3958.4	
Meat	6	2249.8	2276.9	−0.42
	7	4780.8	4769.3	+0.43

Following Rubner, Atwater, at one time a pupil of Voit, with the aid of Rosa, the physicist, constructed a large calorimeter capable of measuring to a nicety the amount of heat given off by a man living in it. This apparatus confirmed Rubner's experiments and has shown that the energy expended by a man in doing any work, such as

[1] Rubner, M.: Sitzungsber. der bayer. Akad., 1885, p. 454.
[2] Rubner, M.: Z. f. Biol., 1894, **30**, 73.

bicycle-riding, is exactly equal to the energy set free by metabolism in the body. *Ex nihilo nihil fit.*

This apparatus was the product of many years of labor and its cost was borne by the United States Government. Armsby completed a similar one for use with cattle for the Agricultural Station of the State of Pennsylvania. Benedict with great success has extended Atwater's work in the notable Nutrition Laboratory of the Carnegie Institution in Boston. This is housed in a building splendidly equipped with apparatus for the simultaneous determination of metabolism and heat production. The work has been still further extended by the construction for the Physiological Laboratory of the Cornell University Medical College in New York City of a small respiration calorimeter[1] suitable for use with babies, dwarfs, and dogs, and of the Sage respiration calorimeter[2] constructed in Bellevue Hospital by the Russell Sage Institute of Pathology for the determination of metabolism in diseased conditions. The latter has been largely under the general management of E. F. DuBois. These elaborate and costly devices prove and confirm the general laws of metabolism in the body enunciated above, through a knowledge of which alone proper systems of nutrition for people under various conditions may be devised (see p. 61). The American Indian when first shown a watch thought it was alive. We, on the other hand, have come to look upon the living organism as a machine. Like the moving locomotive, we burn more if we are to attain a faster speed, or if we are to keep all parts warm in the winter's cold. In both cases the motion and the heat are derived from the power in the fuel. The casual observer sees the moving train, but the expert engineer alone knows how and why the wheels go round. The physiologist busies himself answering the similar how and why regarding the mechanism of living things.

Before taking up the details of the work we may copy the last general pronouncement of Voit[3] upon the subject of metabolism. It reads:

"The unknown causes of metabolism are found in the cells of the organism. The mass of these cells and their power to decompose materials determine the metabolism. It is absolutely proved that

[1] Williams, H. B.: J. Biol. Chem., 1912, **12**, 317.
[2] Riche, J. A., and Soderstrom, G. F.: Arch. Int. Med., 1915, **15**, 805; Lusk, G., *Ibid.*, p. 793.
[3] Voit, C.: Münchener med. Wchnschr., 1902, **49**, 233.

protein fed to the cells is the easiest of all the food-stuffs to be destroyed, next carbohydrates, and lastly fat. The metabolism continues in the cells until their power to metabolize is exhausted. All kinds of influences may act upon the cells to modify their ability to metabolize, some increasing it or others decreasing it. To the former category belong muscular work, cold of the environment (in warm-blooded animals), abundant food, and warming the cells. To the latter, cooling the cells, certain poisons, etc.

"In speaking of the power of the cells to metabolize, I have not meant thereby, as may be seen from all my writings, that the cells must always use energy in order to metabolize, but rather I have understood thereby the sum of the unknown causes of the metabolic ability of the cells—as one speaks of the fermentative 'power' of yeast cells.

"The metabolism of the different food-stuffs varies with the quality and quantity of the food. Protein alone may burn, or little protein and much carbohydrate and fat. I have determined the amount of the metabolism of the various food-stuffs under the most varied conditions. All the phases of metabolism originate from processes in the cells. In a given condition of the cells available protein may be used exclusively if enough be furnished them. If the power of the cells to metabolize is not exhausted by the protein furnished, then carbohydrates and fats are destroyed up to the limit of the ability of the cells to do so.

"From this use of materials arise physical results, such as work, heat, and electricity, which we can express in heat units. This is the power derived from metabolism.

"It is possible to approach the subject in the reverse order, that is, to study the energy production (Kraftwechsel) and to draw conclusions regarding the metabolism (Stoffwechsel). It is perfectly possible to say that the requirement of energy in the body or the production of the heat necessary to cover heat loss, or for energy to do work, are controlling factors of the metabolism; since on cooling the body or on working correspondingly more matter is destroyed. But one must not conclude that the loss of body heat and muscular work are the immediate causes of this increased metabolism. The causes lie in the peculiar conditions of the organism, and muscle work and loss of heat are merely factors acting favorably upon those causes, raising the power of the cells to metabolize. In virtue of this

more is destroyed, and secondarily the power to work and increased heat production are determined.

"The requirement for energy cannot possibly be the cause of metabolism, any more than the requirement for gold will put it into one's pocket. Hence the production of energy has a very definite upper limit, which is afforded by the ability of the cells to metabolize. If the cells will metabolize no more, then further increase of work ceases even in the presence of direst necessity; and this is also the case with the heat production, even though it were very necessary, and we were likely to freeze.

"I therefore maintain my 'older' point of view, that of pure metabolism, in order to explain the phenomena of nutrition. I am convinced that it is the right way, and that the clearest and most unifying development will be possible as one investigates what substances are destroyed under different circumstances, such as the performance of work, and loss of heat, and how much of the different materials must be fed to maintain the body in condition."

CHAPTER II

THE NATURE OF THE FECES

Only by following out the injunction of our great predecessor (Harvey), to search out and to study the secrets of nature by way of experiment, can we hope to attain to a comprehension of the wisdom of the body, and the understanding of the heart, and thereby to the mastery of disease and pain, which will enable us to relieve the burden of mankind.—E. H. Starling, Harveian Oration, 1923.

In the historic introduction just given it has been shown that the nitrogen of the urine and feces can be made a measure for the determination of protein metabolism. It is easy to comprehend that urinary constituents, such as urea, uric acid, the purin bases, creatinin, etc., are derived from the metabolism of flesh in the body, whether the flesh be the body's own or that of an animal fed to it. But the intestinal canal where the feces are formed is a long tube open at both ends, through which may pass the nitrogen gas of the air swallowed and indigestible substances such as hair, tacks, etc. In diarrhea the curds of milk, pieces of undigested meat or bread, and large quantities of fat are in evidence. These common observations would seem to justify the popular supposition that normal feces are made up of the undigested residues of the food-stuffs. In truth, however, this is very far from the fact. The feces are chiefly the unabsorbed residues of intestinal excretions.

The collection of the feces for a given period of nutrition is more difficult than the collection of the urine. The urine may be collected every two hours and may fairly represent the protein metabolism of the time, but the feces are normally passed but once a day by a man on a mixed diet, and only once in five days by a dog fed with meat. Furthermore, particles fed to a man are not usually passed in his feces for two or three days. The feces formed during a certain digestive period might therefore leave the body two or three days after the urine was drawn from the bladder. To obtain clear results Voit fed a dog with 60 grams of bones in a preliminary diet eighteen hours before the regular feeding began. These bones yielded a whitish mark in the fecal excretion. All feces subsequent to the mark

were attributed to the diet used in the experiment. At the conclusion of the experiment a second diet containing bones was given. The whitish excrement formed from this indicated the end of the feces of the period. For the same purpose Rubner[1] gave milk (2 liters) to a man, the last portion of the milk being taken eighteen hours before the commencement of a period of feeding. The milk feces give a distinct whitish dividing line. A teaspoonful of lampblack may also be readily made use of in man and in animals and carmine is also employed. Cremer[2] uses freshly precipitated silicic acid (10 to 25 grams mixed with 40 to 100 grams fat) instead of bones. This gives excellent results, as it avoids the albuminoid nitrogen in the bones, and is of great advantage if the calcium or other ash constituents of the feces are to be determined.

In the fundamental experiments Voit found that a fasting dog weighing 30 kilograms excreted 1.88 grams of dry fecal matter per day, containing 0.15 gram of nitrogen. Evidently these starvation feces are not derived from the food, but must be derived from the matter passed from the body into the intestinal canal. An analogous condition is found in the intestinal tract of the newborn infant. The meconium consists principally of the unabsorbed residues of the bile, of glycocholic, taurocholic, and fellic acids, of cholesterol and lecithin, colored by bilirubin or biliverdin. The absence both of putrefaction and the acid of the gastric juice prevents the breaking up and reabsorption of many of these substances, processes which occur soon after birth. The fasting dog of 30 kilograms, mentioned above, excreted 1.88 grams of dry feces, but a fasting dog of 20.3 kilograms may yield 4.3 grams of dry bile solids through a biliary fistula in twenty-four hours.[3] The ordinary starvation feces therefore cannot consist of the total of the excretions from the body into the digestive tract, but are rather their unabsorbed remainder.

When meat was given, Bischoff and Voit[4] found that the production of feces was not proportional to the amount of meat. A compilation of the data given by Friedrich v. Müller[5] illustrates the average

[1] Rubner, M.: Z. f. Biol., 1879, **15,** 119.
[2] Cremer, M., and Neumayer, H.: *Ibid.*, 1897, **35,** 391.
[3] Voit, C.: *Ibid.*, 1894, **30,** 548.
[4] Bischoff, T. L. W., and Voit, C.: "Die Ernährung des Fleischfressers," Leipzig and Heidelberg, 1860, p. 291.
[5] von Müller, F.: Z. f. Biol., 1884, **20,** 340.

amount of dry feces produced by a dog weighing 35 kilograms after feeding different quantities of meat:

Meat in Grams	Fecal Solids	Fecal N
0	2.0	0.15
500	5.1	0.33
1000	9.2	0.60
1500	10.2	0.66
2000	11.1	0.72
2500	15.4	1.00

The feces had the same pitch-black color as starvation feces and were similar to the 2 grams of feces which would have been produced by the same dog had he been starving. No muscle-fibers and no protein could be detected. It seemed clear that the meat feces differed from the starvation feces mainly in quantity, and that this quantity was larger because the secretions into the intestines had been stimulated by the passing food.

Fat ingested with the meat in moderate quantities had no influence on the feces. Nor had sugar, unless its fermentation produced diarrhea. Bread somewhat increased the volume of the feces, which contained some undigested starch. Here an irritation of the intestinal canal by the bread produced a larger excretion into the intestines (see p. 57).

The source of the feces was further investigated by Hermann,[1] whose work was later elaborated by Fritz Voit.[2] The latter separated a loop of the intestine about a third of a meter long from the rest of the intestine of a starving dog. Both ends of the loop were tied and the loop remained in the abdomen in connection with its normal nerve and blood supply. The two ends of the remaining portion were reunited. After a few days food could be given and the normal excretion of feces took place. After three weeks the animal was killed. It was found that the isolated loop contained a thick, fecal-like mass. It was found that the dry solids of this mass contained the same percentage of nitrogen as did the feces passed by the dog during the three weeks of the experiment. It was also calculated that the amount of nitrogen excreted through the wall of the intestinal loop was nearly the same per unit of area as the amount of nitrogen in the feces when spread over the surface of the whole of the rest of the intestine. The following table shows this:

[1] Hermann, L.: Pflüger's Arch. gesam. Physiol., 1890, **46**, 93.
[2] Voit, F.: Z. f. Biol., 1892, **29**, 325.

	Percentage of N in the Dry Substance		Grams N from 1 Sq. M. in 24 Hours	
	Feces	Content of Loop	Feces	Content of Loop
Dog I	5.62	5.32	0.28	0.22
Dog III	5.27	6.88	0.25	0.32

The loop contained fat and fatty acids in greater quantity than is normally found in feces, which may indicate a usual reabsorption of these substances.

Fritz Voit has therefore shown that the excretion of substances from an isolated loop of the intestine produces a mass of a similar constitution and of nitrogen output equal to that in the normal intestine of the same animal through which meat and fat were passing. He therefore concluded that the feces are derived principally from the substances excreted through the wall of the intestine. The nitrogen so excreted is as much to be considered a product of protein metabolism as is the nitrogen of urea. It is regretable that very little is known regarding the chemistry of these nitrogenous compounds excreted into the intestine.

The work of Hill and Bloor[1] has shown very conclusively that the "fat" in the feces is not the fat of the diet. Cocoanut oil has an iodin number of 8.8 and olive oil one of 88.2. The above named workers have compared the composition of the feces when a person is taking (1) a diet free from fat, (2) a meat diet, (3) a diet containing 50 gm. of cocoanut oil, and (4) a diet containing 50 gm. of olive oil, and have obtained the following results:

	"Fat" in the Feces		Iodin Number
	Gm.	Per Cent	
Fat-free diet	1.76	...	32.7
Meat diet	2.83	7.9	38.1
Diet with cocoanut oil	2.50	6.3	24.8
Diet with olive oil	2.24	4.8	44.6

The fecal fat, both in chemical composition and in quantity, was largely independent of the fat in the diet.

In a second article Sperry and Bloor[2] affirm that fecal "fat" cannot arise directly from unabsorbed fatty materials in the food because in many cases almost as much fatty materials appear in the

[1] Hill, E., and Bloor, W. R.: J. Biol. Chem., 1922, **53**, 171.
[2] Sperry, W. M., and Bloor, W. R.: J. Biol. Chem., 1924, **60**, 261.

feces after taking a diet free from fat as after one containing fat. The chemical composition of food and feces fat is different. The feces fat of fasting is chemically akin to that after a fatty meal. There is a marked similarity between blood and fecal lipoids both in chemical composition and in melting point. If fats of a high or those of a low melting point be administered, they may be absorbed and change the character of the fecal lipoid, but only through their excretion from the blood.

These experiments extend and confirm the doctrines of the older masters.

Sperry[1] finds that when dogs weighing between 5 and 13 kg. are given a diet free from lipoids they excrete in the feces between 1.5 and 2 gm. non-volatile lipoids a week. Of this 35 to 40 per cent. is unsaponifiable material, which Gardner[2] has suggested contains the waste products of cholesterol metabolism, and 55 to 60 per cent. of non-volatile fatty acids, containing stearic, palmitic, and probably oleic acids. Fatty acids, soaps, and cholesterol products make up the bulk of fecal "fat."

Langworthy and Holmes[3] show the "coefficient of digestibility" of various fats as follows:

Cotton seed oil	97.6	Cocoanut oil	97.9
Olive oil	97.8	Sesame oil	98.0
Peanut oil	98.3	Cocoa-butter	94.9

Blunt and Mallon[4] found that 96.7 per cent. of bacon fat was absorbed, and Holmes and Deuel[5] report that hydrogenated cotton seed, peanut, and corn oils, with melting points of from 33° to 43°, are as well digested and absorbed as natural fats, i.e., 95 to 98 per cent. It is quite likely that in truth these fats are completely absorbed, and that the fecal "fat" is derived from the elimination through the intestine of fats, fatty acids, and soaps present in the blood stream. If however the melting point be high as in a hydrogenated peanut oil melting at 52.4° a large amount of undigested fat is found in the feces, the utilization averaging 79 per cent.

[1] Sperry, W. M.: J. Biol. Chem., 1926, **68**, 357.
[2] Gardner, J. A.: Biochem. J., 1921, **15**, 244.
[3] Langworthy, C. F., and Holmes, A. D.: States Relations Service, Bull. 310, 1915; Bull. 505, 1917.
[4] Blunt, K., and Mallon, M. G.: J. Biol. Chem., 1919, **38**, 43.
[5] Holmes, A. D., and Deuel, H. J., Jr.: Am. J. Physiol., 1920–21, **54**, 479.

It has been seen that the feeding of simple food-stuffs, such as meat, fat, and sugar, scarcely influenced the composition of the feces in the dog. In herbivora we pass to another extreme. Here vast amounts of cellulose are eaten, a great part of which is never disintegrated, but even after long retention in the capacious intestinal tract is passed in the feces. After giving an ordinary feed to a cow one may find as much nitrogen in the feces as in the urine. Under such conditions as these the very voluminous feces evidently do consist largely of the undigested residues of the fodder. Armsby and Fries[1] have shown that only 45 per cent. of the energy contained in hay is of actual use in cattle feeding. The waste in the feces reaches 41 per cent., in the urine 7.25, and in methane gas 6.75 per cent. of the total energy content.

Concerning the fecal production in man it has been found that Cetti[2] excreted 3.8 grams of dry fecal solids per day during a fast of ten days, Breithaupt 2 grams, and a medical student[3] 2.2 grams, less in reality than would a dog of similar size. Benedict[4] states that he was unable to find any evidence of the formation of feces during a seven-day fast in man.

Rieder[5] gave a man a diet containing starch, sugar, and lard from which a cake was baked. The food contained no nitrogen, but the fecal excretion was 0.54, 0.87, and 0.78 gram of nitrogen per day, contrasting with 0.316 gram from Cetti, 0.113 from Breithaupt, and 0.13 from a medical student during fasting. The food, even though it contains no protein, stimulates the fecal production.

Wallace and Salomon[6] have administered 250 grams of cane-sugar daily to normal persons and to patients suffering from intestinal diarrhea, and have determined the amount of fecal nitrogen during periods of two or three days. The sugar was given in doses of 50 grams dissolved in 300 c.c. of water and flavored with fruits, such as apple and lemon, or with wine. Their results with this diet were as follows:

[1] Armsby, H. P., and Fries, J. A.: Bureau of Animal Industry, U. S. Dept. of Agriculture, Bull. 101, 1908.

[2] Lehmann, C., Müller, F., Munk, I., Senator, H., and Zuntz, N.: Virchow's Arch. path. Anat., 1893, **131**, Suppl.

[3] Johansson, J. E., Landergren, E., Sondén, K., and Tigerstedt, R.: Skan. Arch. Physiol., 1897, **7**, 29.

[4] Benedict, F. G.: "Influence of Inanition on Metabolism," Carnegie Institution of Washington, Pub. 77, 1907, p. 345.

[5] Rieder, H.: Z. f. Biol., 1884, **20**, 378.

[6] Wallace, G. B., and Salomon, H.: Med. Klin., 1909, **5**, 579.

	N in Feces per Day Grams
Normal man	0.539
" "	0.380
Tuberculous ulceration of intestine	3.075
" " "	4.186
Cancer of intestine	1.74
" "	1.974
Catarrh of intestine (severe)	1.464
" " "	1.087

It is evident that the quantity of fecal nitrogen eliminated in intestinal diseases is largely increased.

It has been stated that Voit early noticed the occurrence of starch particles in the feces. A large number of experiments have been made to test the digestibility of the various vegetables and cereals. Rubner[1] fed an able-bodied soldier on 3078 grams of variously cooked potatoes daily and found pieces of potatoes in the feces. He notes that an inhabitant of Ireland will eat 4500 grams of potatoes a day. Friedrich Müller[2] writes that after the ingestion of a large quantity of bread the feces may have practically the same composition as bread.

The better understanding of this question of the digestibility of the carbohydrates has come through the work of Prausnitz[3] and his associates, Moeller and Kermauner. Moeller found that no starch appeared in the feces after feeding well-cooked white, rye, and graham bread, rice or potatoes (even when fed in pieces), or legumes when they were prepared in the form of purée. Legumes not in the form of purée, such as string beans eaten as salad, may resist the action of the digestive juices so that the starch contents of the cell are untouched, and the vegetable cells appear in the feces. These facts explain the appearance of bread in the feces if the bread be badly cooked, or if such a "heavy" bread as pumpernickel be eaten. The imperfectly cooked bread contains starch granules whose coverings are impermeable to the digestive juices, as are also many of those in the unbolted rye of pumpernickel.

Prausnitz finds that if a man be put on a rice diet and then meat be substituted for most of the rice, the composition of the feces does not vary with the diet. Such feces he calls *normal feces*. They may contain a negligible quantity of fibers of meat or of cellulose from the rice.

[1] Rubner, M.: Z. f. Biol., 1879, **15**, 146.
[2] Müller, Fr.: *Ibid.*, 1884, **20**, 375.
[3] Prausnitz, W.: *Ibid.*, 1897, **35**, 335.

The feces of 6 persons placed alternately on meat and rice diets yielded normal feces, the percentage composition of the dry solids of which was as follows:

COMPOSITION OF FECES ON DIFFERENT DIETS

No.	Person	Principal Food	N Per Cent.	Ether Extract Per Cent.	Ash Per Cent.
1	H.	Rice	8.83	12.43	15.37
2	H.	Meat	8.75	15.96	14.74
3	M.	Rice	8.37	18.23	11.05
4	M.	Meat	9.16	16.04	12.22
5	W. P.	Rice	8.59	15.89	12.58
6	W. P.	Meat	8.48	17.52	13.13
7	J. Pa.	Rice	8.25	.....	14.47
8	J. Pa.	Meat	8.16	.....	15.20
9	F. Pi.	Rice	8.70	.....	16.09
10	F. Pi.	Meat	9.05	.....	15.14
11	Vegetarian.	Rice	8.78	18.64	12.01
		Average,	8.65	16.39	13.82

It is seen from this that whether the food solids contain 1.5 per cent. N, as in rice, or ten times that, as in meat, the composition of the feces remains uninfluenced. Normal feces result from the eating of any food which is completely digested and absorbed. In all such cases these feces have the same composition and are derived from the intestinal wall. It is therefore not astonishing that a vegetarian of many years' standing produced the same kind of feces when fed on rice as did the other men. The same quality of feces has been obtained after giving good bread.

In this connection it is interesting to note that the heat value of 1 gram of dry human feces is very constant whether the person is on a meat diet or a medium mixed diet. Rubner[1] gives the heat value of 1 gram of organic matter in the feces of a man on a meat diet at 6.403 cals., while on a mixed diet 1 gram varies between 6.061 and 6.357 cals. After a diet poor in fat 1 gram may contain 6.104 cals. and after one rich in fat 6.059 cals.[2] The average fuel value of feces is therefore 6.2 calories per gram of dry organic substance, and this changes only when there is a poor utilization of the food.[3] According to Lohrisch,[4] one may calculate the approximate heat value of feces by reckoning the nitrogen therein as protein nitrogen and multiplying the amounts of "protein," "fat," and "carbohydrate" present by their usual heat

[1] Rubner, M.: "Die Gesetze des Energieverbrauchs bei der Ernährung," Leipzig and Vienna, 1902, p. 35.

[2] Rubner, M.: Z. f. Biol., 1901, **42**, 261.

[3] Rubner, M.: E. v. Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, 2d ed., p. 32.

[4] Lohrisch, H.: Z. physiol. Chem., 1904, **41**, 308.

value. The sum of these is said to give a good estimate of the calorific loss through the feces (see pp. 41, 74).

After eating pumpernickel, bad bread, or string beans the waste of undigested residues of these substances may appear in the feces, changing its composition and lowering its percentage of nitrogen content.

In general, Prausnitz finds no difference between the digestibility and absorbability of animal and vegetable foods. Meat, rice, and bread from flour are all digested and absorbed. The ordinary feces indicate whether a given food is a small or a great feces builder, not how much or how little food has been used for the organism.

The value in such foods as cabbage, string beans, cauliflower, and the like lies, aside from their flavor, in the fact that their indigestible waste may enhance peristalsis in the intestine. Their food value is small, and if given to those with weak digestions, is dubious. Mendel[1] points out that edible carbohydrate substances, like Iceland moss, agar-agar, Jerusalem artichokes, and inulin, are scarcely attacked by the digestive juices and therefore have little or no direct nutritive function. He[2] also finds that the proteins of mushrooms are not digested in the organism.

The part played by bacteria in the composition of the feces has been variously estimated. Lissauer,[3] working in Rubner's laboratory, showed that two-thirds of the fecal solids were soluble in alcohol. In the insoluble portion mucin, food protein, and the remnants of cast-off epithelial cells, as well as bacteria were found. When a diet of meat was given to a man food residues were almost entirely wanting in the feces. Though the quantity of bacteria may be of importance in the stools, it is an insignificant factor when compared with the total quantity of food ordinarily ingested. Lissauer finds the following percentages of bacteria in stools of the character noted below:

	Food	Percentage of Dry Bacterial Substances in Dry Fecal Material
In Man	Meat	4.3
	Mixed	8.7
	Vegetable	10.5
In Dogs	Meat	5.4
	Potatoes and bread	7.6
In Rabbits		1.0
In Cows		16.7

[1] Mendel, L. B.: Zentralbl. f. Stoffwech., 1908, **3**, 641.
[2] Mendel, L. B.: Am. J. Physiol., 1898, **1**, 225.
[3] Lissauer, M.: Arch. f. Hyg., 1906, **58**, 145.

In man the minimal quantity of bacteria composing the stools was 2.53 per cent., the maximum 13.54 per cent., and the average was 8.7 per cent. of the total solids. Rubner has calculated that 1 gram of dry bacterial substance contains 0.114 gram nitrogen. Making use of these data, Lissauer has prepared the following table to illustrate the part which bacteria may play in the fecal nitrogen elimination of man:

Diet	Dry Feces Gram	N Gram	Bacteria Gram	Bacterial N Gram
Meat	17.1	1.12	0.73	0.08
Mixed	30.0	2.9	2.86	0.33

It is evident that the quantity of bacterial nitrogen in the feces is small in comparison with the ordinary intake of nitrogen in the food. Though the feces apparently swarm with bacteria, it should be recalled that 4,000,000,000 weigh only 1 milligram.

It may be added that Osborne and Mendel[1] report that 70 per cent. of the nitrogen of the rat's feces is due to bacteria and Schwarz[2] reports that in the colon of herbivora the nitrogen partition is as follows:

16 per cent. in bacteria
24 per cent. in infusoria
25 per cent. in soluble form
35 per cent. in food rests.

WAR WORK OF RUBNER ON THE DIGESTIBILITY OF BREADS AND OTHER FOODS, AS DETERMINED BY ANALYSIS OF THE FECES

During the World War Rubner, at the behest of the German Government, took up the subject of the nutritive value of various breads, though on account of his own accurate scientific knowledge he was personally pessimistic over the immediate practical value of his labors. In 1916 he published an article "On the Digestibility of White Bread." In this he states that the millers of the Eighteenth Century had to be curbed by law for the admission of too much bran into the bread they sold. The year of 1882 was that of the "Bread Reform League" in England and was the time when Liebig, in Munich, held the opinion that milling removed necessary salts and decreased the digestibility of bread. In 1883 Rubner[3] showed Liebig this was not so, that poor utilization was associated with the degree

[1] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1914, **18**, 177.
[2] Schwarz, C.: Pflüger's Arch. gesam. Physiol., 1926, **213**, 571.
[3] Rubner, M.: Z. f. Biol., 1883, **19**, 45.

of milling above a rate which yielded 70 per cent. of flour and that the N in bran was very poorly utilized by human beings, although it was an excellent food for cattle and therefore should be used in agriculture.

During the war demands were made for improving the bread, for the production of a super-bread. The desire to increase the little available, especially of bread, became paramount. Half forgotten things were presented as new ideas. Science was accused of having been culpably negligent. This was unjust, for the work on these problems belonged to an era nearly fifty years before so that the literature and the experiments were entirely unknown even among educated physicians. To many the agitation for an improved bread appeared epoch making, but for the great mass of the people the fundamental considerations were *palatability* and *low cost*. The vendors of patent foods sought to reap a harvest for themselves, and to expose and check these was the useful but thankless task of experts in nutrition. Famines in Russia have been of historical record since the Eleventh Century, and during these moss, roots, sunflowers, straw, grass seeds, and wood fiber up to 25 to 33 per cent. have been used to extend the bread. The combinations were often wellnigh inedible. Under the auspices of official laymen such fashions were introduced in Germany.[1] This outline was taken from Rubner's account.

On account of the failure of the potato crop of 1916 the first half of 1917 was the "turnip period" in beleaguered Germany. Every effort was made to modify the bread. It seemed astonishing, perhaps, that out of all this agitation nothing developed to equal bread made from wheat milled at 70 per cent.[2]

Rubner gave to a man 465.4 gm. of white bread daily for three days and compared the feces of the period with the feces of a similar period after giving to the same man 478 gm. of whole wheat bread. He found that whole wheat meal contained 11 per cent. of cell membrane. The digestibility of flour depends on this quantity of cell membrane. Fine wheat flour contains only 1.3 per cent. of cell membrane. Cell membrane contains 46 per cent. of pentosans, and in this association the pentosans are not well absorbed, though under ordinary circumstances they are completely absorbed. The experimental results are as follows:

[1] Rubner, M.: Arch. f. Physiol., 1919, p. 1.
[2] Rubner, M.: *Ibid.*, 1916, p. 61.

	White Bread, Gm.	White Bread Feces, Gm.	Whole Wheat Bread, Gm.	Whole Wheat Bread Feces, Gm.
Amount dry substance	465.4	18.3	478.0	44.1
N	8.7	1.07	9.65	2.04
Calories	1825	82	1830	204
Pentosans	15.2	0.96	29.6	9.9
Cellulose	5.8	1.27	7.0	6.9

It is evident from this that the extra gram of N in the whole wheat bread is not serviceable in nutrition but appears as fecal nitrogen. Of the energy content of white bread 4.5 per cent. appears in the feces, and of whole wheat bread, 11.5 per cent. In other words, the loss in calories in the feces is 7 per cent. greater with whole wheat bread than with white bread. Rubner acknowledges the validity of the vitamin doctrine, but since no one lives on bread alone, he does not consider bran necessary to life, and in virtue of its waste in the intestinal tract of the human being, he advocates its use for cattle.

To war bread, straw and sawdust were experimentally added in order to extend its nutritive value, and an analysis of the physiological result was undertaken. Thomas and Pringsheim,[1] in Rubner's laboratory, find that filter paper (pure cellulose) is not digested by a dog, but 22 per cent. may be digested by a rabbit and 57 per cent. by a sheep. Treatment with alkali reduced its digestibility one-half in these animals. The digestion is due to bacteria.

Rubner[2] gave 1000 gm. of horse meat to a dog and added 70 gm. of a dry sawdust preparation previously treated with hydrochloric acid. After giving meat alone the feces contained 1.09 gm. of N; after adding 70 gm. of sawdust containing 0.17 gm. N the fecal N rose to 2.75 gm. The cellulose was entirely undigested. The feces when meat alone was given contained 67.7 calories; after adding the sawdust which contained 260 calories the feces of the period contained 258 calories. Hence the sawdust caused an increased loss through the feces of 190 calories, or 73 per cent. of the quantity ingested. It is therefore impossible to convert wood by treatment with acid into a food capable of being utilized.

Again Rubner[3] tested upon men the value of fine white flour, 90 per cent., to which was added straw meal, 10 per cent., the latter

[1] Thomas, K., and Pringsheim, H.: Arch. f. Physiol., 1918, p. 25.
[2] Rubner, M.: Arch. f. Physiol., 1916, p. 40; 1917, p. 20.
[3] Rubner, M.: *Ibid.*, 1917, p. 74.

having been treated with 10 per cent. sodic hydrate at 4 atmospheres. The quality of the bread suffered both as to its smell and taste. It dried rapidly and required more saliva; it excited the production of intestinal gas; and increased the intestinal excretions. If the feces of the straw-bread be compared with that of white bread, it is found that not only is there an increased loss of N in the feces, but also there is an increased loss of calories which exceeds the total caloric value of the added straw. These results were obtained from strong men. Such stuff is not food for weak stomachs nor for the aged. Nor can whole wheat bread with but little of the bran removed be desirable food for the population.

The American food faddist who would have incorporated into the permanent law of the land the compulsory production of whole wheat bread and its infliction upon the population meets here his nemesis. The British people during the war felt that whatever else happened they would return to white bread as soon as they possibly could. Here instinct, supported by science, triumphs once again over ignorance and bigotry.

Rubner[1] finds that rye bread is as well digested as wheat bread, a fact which is important for the peoples of Europe.

Rubner and Thomas[2] have put together a summary of work done regarding the digestibility of potatoes, and they also present a new experiment in which a daily average of 2618 gm. (2681 cals.) of boiled potatoes, with 10 gm. of common salt, were given to a laboratory servant of powerful physique and weighing 78 kg. who had just returned from the battle front in 1917. The food was easily eaten. The following historical resumé of similar work is given:

	Length in Days	Calories in Potatoes per Day	Loss in Feces	
			Calories Per Cent.	N Per Cent.
Rubner, 1877[3]	3	3011	14.0	32
Rubner and Thomas, 1917	6	2681	6.7	28
Hindhede, 1912[4]	40	2469	4.4	19
Rubner, 1902[5]	3	2294	4.0	
Rubner, 1902[5]	3	2076	5.6	15
Constantinidi, 1887[6]	..	1753	7.0	20

[1] Rubner, M., and Thomas, K.: Arch. f. Physiol., 1916, p. 165.
[2] Rubner, M., and Thomas, K.: *Ibid.*, 1918, p. 1.
[3] Rubner, M.: Z. f. Biol., 1879, **15**, 146.
[4] Hindhede, M.: Skan. Arch. Physiol., 1912, **27**, 277.
[5] Rubner, M.: Z. f. Biol., 1901, **42**, 273.
[6] Constantinidi, A.: Z. f. Biol., 1887, **23**, 453.

Both Rubner and Constantinidi showed that nitrogen equilibrium (see p. 453) could be established with potatoes alone. Rubner[1] criticises Hindhede for having contributed little that was new and for having neglected the citation of the older work.

Rubner[2] reports the following results after giving fruit:

	In Diet		4th Day of Diet		
	Cals.	N Gm.	Urine N Gm.	Feces N Gm.	± Body N Gm.
Strawberries, 2400 gm. (883 cals.) + sucrose, 230 gm., + milk, 30 gm.	1808	2.98	3.49	2.73	−2.98
Apples, 2400 gm.	1524	1.71	5.2	2.4	−5.9

The following summary of Rubner's work[3] upon the subject of the digestibility of cereal and vegetable foods is given by him:

	Per Cent. of Cell Membrane in Food	Loss in the Feces	
		Cals. Lost Per Cent.	N Lost Per Cent.
Fine wheat flour	2.7	4.4	18.7
White rice	....	5.6	20.4
Potatoes	5.6	5.6	15.3
Wheat 70 per cent. milled	8.1	7.7	24.6
Rye 65 per cent. milled	....	9.8	37.8
Same +20 per cent. potato flour	....	9.8	42.5
Wheat 80 per cent. milled	....	11.0	21.1
Rye 72 per cent. milled	....	11.7	39.7
Rye 82 per cent. milled	....	13.5	40.3
Wheat 95 per cent. milled	....	14.0	30.5
Rye 95 per cent. milled	....	14.8	35.1
Rye (*Schwarzbrot*)	....	17.7	32.0
Turnips	22.2	21.8	65.1
Strawberries	18.8	32.8	91.3

He says that it is easy to select foods which show a loss in the feces of less than 8 per cent. of the calories of the diet. In general the loss is proportional to the cell membrane content of the diet and consists of two factors, the cell membrane itself and the products of the stimulation of the intestinal wall. This excess represents waste for the drain pipes.

Finally Rubner[4] has contrasted the formation of feces after giving to a dog approximately 1000 calories in meat, in war bread, and in potatoes, also half portions in meat and war bread mixed, in potatoes and bread mixed, and in potatoes and meat mixed. He confirms his

[1] Rubner, M.: Arch. f. Physiol., 1918, p. 16.
[2] Rubner, M.: *Ibid.*, 1916, p. 237.
[3] Rubner, M.: *Ibid.*, 1918, p. 53.
[4] Rubner, M.: *Ibid.*, 1918, p. 135.

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older work which showed that the addition of fat or sugar to these materials has little influence on the composition of the feces. The potato-meat diet showed the best absorption. The values are as follows:

TABLE SHOWING THE INFLUENCE OF THE COMPOSITION OF THE DIET UPON THE COMPOSITION OF THE FECES. THE FIGURES IN PARENTHESES AND ITALICS REPRESENT IN PER CENT. THE FRACTIONS OF THE FOOD VALUES WHICH APPEAR IN THE FECES

	Food				Feces				
	Dry	Cals.	N	Pento-sans	Dry	Cals.	N	Pento-sans	Starch
	Gm.		Gm.	Gm.	Gm.		Gm.	Gm.	Gm.
Meat, 900 gm.....	205.6	1108	28.24	0.82	7.2	30.5 *(2.74)*	0.42 *(1.49)*	0.09	
War bread, 380 gm...	229.7	970	3.88	22.44	28.1	116. *(12.)*	0.74 *(19.)*	5.90 *(26.3)*	3.7 *(3.2)*
Potatoes, 900 gm.....	232.9	923	2.98	8.43	22.8	91.4 *9.9*	0.61 *(20.5)*	0.76 *(9.)*	2.4 *(1.4)*
Meat, 450 gm. + war bread, 190 gm.	217.6	1039	16.11	11.63	24.4	72.1 *(6.9)*	0.73 *(4.5)*	2.60 *(23.)*	1.4 *(1.7)*
Potatoes, 450 gm. + bread, 190 gm.	238.4	972	3.49	15.34	19.2	82.9 *(8.5)*	0.51 *(14.6)*	2.52 *(16.4)*	4.33 *(2.4)*
Potatoes, 450 gm. + meat, 450 gm.	231.9	1066	15.78	5.08	11.5	50.3 *(4.7)*	0.56 *(3.5)*	0.35 *(6.9)*	1.10 *(1.4)*

The potato-meat figures given above are those of the experiment showing the best absorption.

From a further analysis of the foregoing table Rubner concluded that a mixture of two equal half portions of food produces feces which are attributable to the sum of feces-producing power of each component. That is to say, that each kind of food has its independent action in producing feces. The figures appear in the table.

TABLE SHOWING THE COMPOSITION OF THE FECES AND INDICATING THAT MIXTURES OF TWO FOODS PRODUCE FECES SIMILAR TO THE SUM OF EACH WHEN TAKEN ALONE

	Meat, 900 Gm.	War Bread, 380 Gm.	Potatoes, 900 Gm.	Bread, 190 Gm. + Meat, 450 Gm.		Bread, 190 Gm. + Potatoes, 450 Gm.		Potatoes, 450 Gm. + Meat, 450 Gm.	
	Found	Found	Found	Theory	Found	Theory	Found	Theory	Found
Calories...	30.5	116.	91.4	73.3	72.1	109.	82.9	65.7	50.3
N, gm.	0.42	0.74	0.61	0.58	0.73	0.72	0.51	0.56	0.56
Pentosans, gm.	0.09	5.90	0.76	3.00	2.60	3.33	2.52	0.43	0.35

During the period of the Great War many workers in many lands sought to determine the digestibility of various foods, but the outstanding contribution in this direction seems to belong to Professor Max Rubner, of the University of Berlin.

CHAPTER III

THE ATWATER-ROSA RESPIRATION CALORIMETER

My custom in the matter of chemical experiments is never to believe any of them until I have made experiments myself and tested them.—Carl Wilhelm Scheele (b. 1742).

A respiration calorimeter is an apparatus designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it, and the simultaneous measurement of the quantity of heat produced by that organism.

In 1892 Atwater began work upon a calorimeter which could measure the heat production in man, the first description of which appeared in 1897.[1] The initiative in the undertaking rested with Atwater, whereas the successful completion of the apparatus was largely due to the physicist Rosa. The original Atwater-Rosa calorimeter was combined with a respiration apparatus of the type designed by Pettenkofer, which measured only the carbon dioxid excretion without determining the oxygen intake.

The apparatus represented technical perfection,[2] as was evidenced by the fact that when a measured amount of heat was generated by an electric current within the box it was determined as 100.01 per cent. of the actual value. This test of accuracy is called an *electric check*. Also, when a known quantity of alcohol was oxidized, the carbon dioxid recovered amounted to 99.8 per cent. and the heat to 99.9 per cent. of the theoretic value. This is an *alcohol check*. In experiments with men the work frequently lasted during a period of several days. The method of computation was based on that of Voit and Rubner, *i. e.*, the amount of *protein carbon* excreted was calculated from the nitrogen excreted in the urine and feces, this subtracted from the total carbon excreted in the respiration, urine, and feces gave the *total non-protein carbon* or that attributable to carbohydrate and fat. It was assumed that all the carbohydrate ingested was oxidized and that after deducting this amount the excess of non-protein carbon was derived from the metabolism of fat.

[1] Atwater, W. O., and Rosa, E. B.: Report Storrs Agricul. Exper. Sta., 1897, p. 212.
[2] Atwater, W. O., and Benedict, F. G.: Mem. Nat. Acad. Sc., 1902, **8**, 231.

In this way the calories from protein, carbohydrate, and fat were computed. The validity of this method is shown in the work of Atwater and Benedict by the average results per day of forty days of experimentation with three different individuals who took an ordinary mixed diet:

	Calories
Indirect calorimetry	2717
Direct calorimetry	2723
Difference	0.2 per cent.

Atwater was not content to omit the determination of oxygen, and turned his attention to this important problem. As already explained (p. 29), the quantity of oxygen required in metabolism depends on the kind of material oxidized in the organism, and the relation between the amount of oxygen absorbed and carbon dioxid eliminated depends on the same factor. The ratio of the *volume* of carbon dioxid expired to the *volume* of oxygen inspired during the same interval of time was called by Pflüger the *respiratory quotient.*

It was known to Lavoisier that any volume of oxygen uniting with carbon produced the same volume of carbon dioxid. Since the volume of oxygen inspired was found in his experiments to be larger than that of the expired carbon dioxid, Lavoisier concluded that a portion of the inspired oxygen must have been used to oxidize hydrogen in the production of water. Under these circumstances the $\frac{\text{Volume } CO_2}{\text{Volume } O_2}$ would be less than unity. The carefully executed experiments of Regnault and Reiset, published in 1849, showed that the value of the respiratory quotient depended on the nature of the food given and not on the species of animal. They found that the respiratory quotient might vary in the same animal from 1.02 to 0.64, and that it varied with the kind of food taken, but was constant with the same food. When fowls were fed with corn or dogs with bread, respiratory quotients of 1.02 and 0.93, respectively, were obtained. The quotients were lower when a meat diet was given and still lower than this when the animal fasted. The low quotients during inanition were obtained alike with herbivorous and carnivorous animals, which indicated to Regnault and Reiset that these animals lived upon their own flesh under conditions not unlike those existing when a meat diet was taken (see p. 25).

Turning now to modern analysis, it is evident that when carbohydrate, in which hydrogen and oxygen are always present in the

proportion to form water, is oxidized, the respiratory quotient will be unity. One may express the process thus:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$$

Since equal volumes of gases at the same temperature and pressure contain equal numbers of molecules (Law of Avagadro, 1811) it is evident from the above formula that one volume of oxygen absorbed produces one volume of carbon dioxid during carbohydrate combustion. Hence, for carbohydrate the R. Q. = 1.00.

When fat is oxidized oxygen is utilized not only for the production of carbon dioxid, but also for the oxidation of hydrogen, forming water.

This is evident from the following formula:

$$C_3H_5(O_2C.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_3)_3$$
Tripalmitin

If one deducts the intramolecular water from tripalmitin one obtains the following:

Tripalmitin	$C_{51}H_{98}O_6$
Deduct intramolecular H_2O	$H_{12}O_6$
Leaving for oxidation	$C_{51}H_{86}$

This on oxidation yields:

$$2(C_{51}H_{86}) + 145O_2 = 102CO_2 + 86H_2O$$

$$\text{R. Q.} = \frac{102 \text{ volumes } CO_2}{145 \text{ volumes } O_2} = 0.703$$

Edible fats are usually mixtures of various simple fats, consisting for the most part of tripalmitin, tristearin, and triolein, all of which require nearly the same quantity of oxygen for oxidation. Lehmann, Müller, Munk, Senator, and Zuntz[1] analyzed the respiratory quotient which should be obtained from lard as follows:

1 gram lard	= 0.765 g.	C + 0.119 g.	H + 0.116 g. O
Deduct intramolecular water		0.0145 g.	H + 0.116 g. O
	0.765 g.	C + 0.1045 g.	H
Required for oxidation	2.040 g.	O + 0.836 g.	O
	2.805 g.	CO_2 + 0.9405 g.	H_2O

As the weight of the oxygen molecule is to that of carbon dioxid as 8 is to 11, the respiratory quotient is deduced from the relative weights as follows:

$$\text{R. Q.} = \frac{2.805 \text{ g. } CO_2}{2.876 \text{ g. } O_2} \times \frac{8}{11} = 0.709$$

[1] Lehmann, C., Müller, F., Munk, I., Senator, H., and Zuntz, N.: Virchow's Arch. path. Anat., 1893, **131**, Suppl., p. 51.

Zuntz[1] later slightly changed the oxygen value so that the calculated quotient was 0.707. A computation by Zuntz[2] for human fat shows a respiratory quotient of 0.713. The respiratory quotient of fat is, therefore, very constant.

The respiratory quotient for protein is, for the most part, the resultant of the oxidation of the various amino-acids of which protein is composed (see p. 83). This quotient, as calculated by Zuntz, is based upon the careful analytic data prepared by Rubner, already described. Zuntz, however, subtracted the fat in the feces from the material attributable to protein metabolism. A computation by Loewy[3] is as follows:

100 grams meat protein contain:	52.38 g. C	7.27 g. H	22.68 g. O	16.65 g. N	1.02 g. S
of which is eliminated—					
in the urine:	9.406 g. C	2.663 g. H	14.099 g. O	16.28 g. N	1.02 g. S
in the feces:	1.471 g. C	0.212 g. H	0.889 g. O	0.37 g. N	
leaving a residuum for the respiratory process of—	41.50 g. C	4.40 g. H	7.69 g. O		
deduct intramolecular water:		0.961	7.69		
	41.50 g. C	3.439 g. H			

These quantities of carbon and hydrogen would require 138.18 grams of O_2 and produce 152.17 grams of CO_2.

One gram of carbon dioxid occupies a volume of 0.5059 liters at a temperature of 0° and 760 mm. pressure.[4] Since *carbon dioxid* does not act like a perfect gas, it has been found that *one gram* in dilute concentration and determined gravimetrically at 20° to 25° would occupy a volume of 0.5094 liters at 0° and 760 mm. pressure, and one liter would weigh 1.963 grams.

As oxygen does act like an almost perfect gas, a liter weighing 1.42897[5] grams at 0° and 760 mm., it may be calculated that *one gram* occupies a volume of 0.6998 liters.[6]

Since 1 gram of oxygen is the equivalent of 0.6998 liter and 1 gram of carbon dioxid amounts to 0.5094 liter, the R. Q. for meat protein would be $\frac{77.52 \text{ liters } CO_2}{96.70 \text{ liters } O_2} = 0.80160$. From these data it may be calculated that for every gram of urinary nitrogen derived from protein 8.49 grams of oxygen are required for the oxidative

[1] Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1897, **68,** 201.

[2] Zuntz, N.: Zuntz und Loewy's "Lehrbuch der Physiologie des Menschen," Leipzig, 2d ed., 1913, p. 644.

[3] Loewy, A.: Oppenheimer's "Handbuch der Biochemie," Jena, 1911, **4,** 1, 279.

[4] Baxter, G. P.: J. Am. Chem. Soc., 1923, **45,** 564.

[5] Baxter, G. P., and Starkweather, H. W.: Proc. Nat. Acad. Sc., 1924, **10,** 479.

[6] I am indebted to Dr. Walter M. Boothby for calling my attention to these factors and to Dr. Geo. Shannon Forbes, of Harvard University, for providing the accurate data. Also to Mr. Max Kriss for showing me that 1 gm. urinary N = 8.49 gm. inspired O_2 and *not* 8.45 gm. erroneously given in the Third Edition.

Analysis of the Oxidation of Mixtures of Carbohydrate and Fat.

R. Q.	Percentage of total oxygen consumed by:		Percentage of total heat produced by:		Calories per liter O_2.	
	Carbohydrate. (1)	Fat. (2)	Carbohydrate. (3)	Fat. (4)	Number. (5)	Logarithm. (6)
0.707	0	100.0	0	100.0	4.686	0.67080
0.71	1.02	99.0	1.10	98.9	4.690	0.67114
0.72	4.44	95.6	4.76	95.2	4.702	0.67228
0.73	7.85	92.2	8.40	91.6	4.714	0.67342
0.74	11.3	88.7	12.0	88.0	4.727	0.67456
0.75	14.7	85.3	15.6	84.4	4.739	0.67569
0.76	18.1	81.9	19.2	80.8	4.751	0.67682
0.77	21.5	78.5	22.8	77.2	4.764	0.67794
0.78	24.9	75.1	26.3	73.7	4.776	0.67906
0.79	28.3	71.7	29.9	70.1	4.788	0.68018
0.80	31.7	68.3	33.4	66.6	4.801	0.68129
0.81	35.2	64.8	36.9	63.1	4.813	0.68241
0.82	38.6	61.4	40.3	59.7	4.825	0.68352
0.83	42.0	58.0	43.8	56.2	4.838	0.68463
0.84	45.4	54.6	47.2	52.8	4.850	0.68573
0.85	48.8	51.2	50.7	49.3	4.862	0.68683
0.86	52.2	47.8	54.1	45.9	4.875	0.68793
0.87	55.6	44.4	57.5	42.5	4.887	0.68903
0.88	59.0	41.0	60.8	39.2	4.899	0.69012
0.89	62.5	37.5	64.2	35.8	4.911	0.69121
0.90	65.9	34.1	67.5	32.5	4.924	0.69230
0.91	69.3	30.7	70.8	29.2	4.936	0.69339
0.92	72.7	27.3	74.1	25.9	4.948	0.69447
0.93	76.1	23.9	77.4	22.6	4.961	0.69555
0.94	79.5	20.5	80.7	19.3	4.973	0.69663
0.95	82.9	17.1	84.0	16.0	4.985	0.69770
0.96	86.3	13.7	87.2	12.8	4.998	0.69877
0.97	89.8	10.2	90.4	9.58	5.010	0.69984
0.98	93.2	6.83	93.6	6.37	5.022	0.70091
0.99	96.6	3.41	96.8	3.18	5.035	0.70197
1.00	100.0	0	100.0	0	5.047	0.70303

Formula for Column (R. Q. = R)

(1) % $= 100 \dfrac{R - 0.707}{0.293}$

(2) % $= 100 \dfrac{1.00 - R}{0.293}$

(3) % $= \dfrac{504.7\ (R - 0.707)}{5.047\ (R - 0.707) + 4.686\ (1.00 - R)}$

(4) % $= \dfrac{468.6\ (1.00 - R)}{5.047\ (R - 0.707) + 4.686\ (1.00 - R)}$

(5) Calories $= 4.686 + \dfrac{R - 0.707}{0.293} \times 0.361$

(6) Logarithm = log of Column 5

process and 9.35 grams of carbon dioxid are eliminated in virtue of such oxidation.

In consequence of this, one may estimate the substances oxidized in the organism by deducting from the total elimination of carbon dioxid the quantity derived from protein (grams urinary N × 9.35), and from the total oxygen absorbed that required to oxidize protein

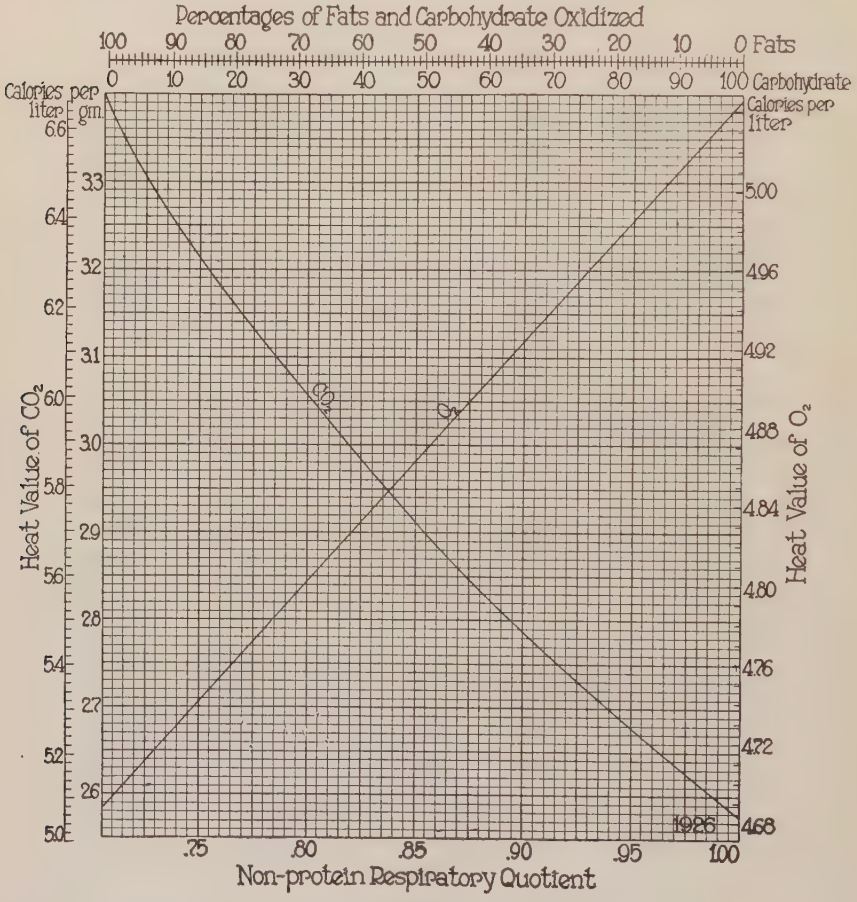


Fig. 1.

(grams urinary N × 8.49). From the figures so obtained one determines the *non-protein* R. Q. From this the part played by fat and carbohydrate in metabolism may be computed. For when fat alone is oxidized the quotient will be 0.707, and when carbohydrate is oxidized it will be 1.00. Quotients which are intermediary between these two indicate that mixtures of the two materials are being

destroyed (see p. 65). Knowing the quantities of these gases, their relative volumes (the R. Q.), and also the nitrogen elimination, it is possible to calculate exactly what amounts of protein, carbohydrate, and fat have been oxidized during the period of experimentation.

The R. Q., therefore, ranges from 0.707 for fat to 1.00 for carbohydrate. Exceptions may be noted under conditions involving the conversion of carbohydrate into fat in which case the quotient exceeds unity (see p. 396) and in severe diabetes, when the quotient may be less than 0.707 (see p. 670).

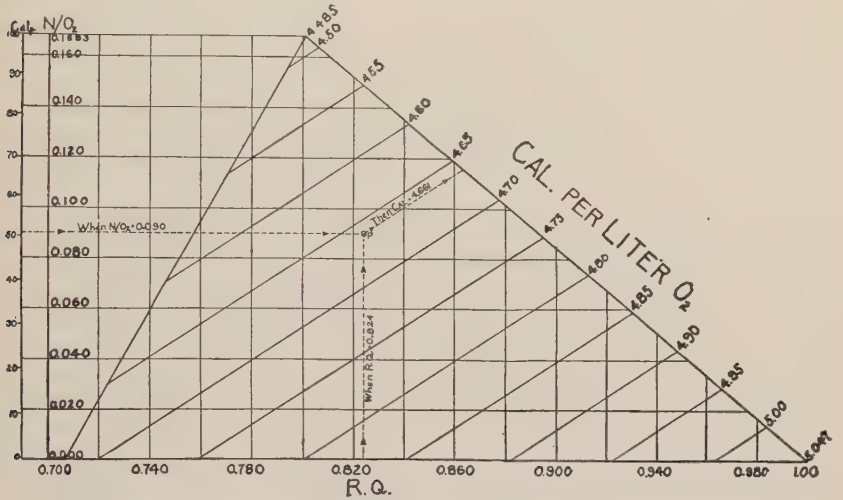


Fig. 2.—Chart showing the calorific value of a liter of oxygen according to the total R. Q. and the relationship of urinary nitrogen and total oxygen consumption (Michaelis).

The table on page 65 published by Lusk[1] is a modification of that given by Zuntz and Schumburg.[2] Samuel Brody has ingeniously plotted the table in the form of a chart (Figure 1). Michaelis,[3] when a Cornell medical student, devised a diagram (Fig. 2) from which it is possible to compute the metabolism if (1) the urinary nitrogen, (2) the number of grams of oxygen inspired, and (3) the R. Q. are known. Thus in the experiment given on page 68 one may calculate as follows:

$$\frac{0.136 \text{ gm. N}}{6.17 \text{ gm. } O_2} = 0.022.$$

From the value 0.022 and the R. Q. of 0.79 it appears that 1 liter of inspired O_2 has a caloric value of 4.75 calories. Since 6.17 gm. O_2 ×

[1] Lusk, G.: J. Biol. Chem., 1924, **59**, 41.

[2] Zuntz, N., and Schumburg, H.: "Studien zu einer Physiologie des Marsches," Berlin, 1901, p. 361.

[3] Michaelis, A. M.: J. Biol. Chem., 1924, **59**, 51.

0.7 = 4.32 liters O_2, the total heat production will be 4.32 × 4.75 or 20.52 calories instead of 20.43 calories, computed by the other method.

From this analysis of the oxidative process associated with the destruction of carbohydrate, fat, and protein in the organism, it is possible to compute the heat value of the respiratory gases when the various substances are oxidized. This knowledge may be compressed into the following table given by Loewy:[1]

1 Gram Substance	O_2 Absorbed	CO_2 Formed	R. Q.	Calories	Calories	
					1 Liter O_2	1 Liter CO_2
	C.C.	C C.				
Protein*	967.0	775.2	0.802	4.316	4.463	5.567
Fat	2019.3	1427.3	0.707	9.461	4.686	6.629
Starch	828.8	828.8	1.000	4.182	5.047	5.047

* Revised values.

Recent caloric values of the liter of oxygen utilized are given by Benedict and Fox[2] as follows:

CALORIES PER LITER OF INSPIRED OXYGEN

Sucrose	5.08	Animal fat	4.72	Protein	4.60
Lactose	5.00	Human fat	4.79	Beef stew	4.84
Starch	5.06	Butter fat (min.)	4.62	Mince pie	4.97
Glucose	5.01	Beta-oxybutyric acid.	4.85	Various sandwiches	4.95
Lactic acid	4.85	Ethyl alcohol	4.85	Doughnut	4.90

Based upon the analytic figures given for protein, Loewy computed that:

1 gram urinary nitrogen = 26.51 calories.

An example of the calculation of indirect calorimetry may be of value as an illustration. The subject was a dog weighing 12.75 kilograms and the period was one hour in duration. The calories directly determined by the calorimeter are also given:

	CO_2 Grams	O_2 Grams	R. Q.	Urine N Grams
Respiratory exchange	6.75	6.17	0.79	0.136
Deduct protein (0.136 × 9.35) = 1.27		(0.136 × 8.49) = 1.15		
Non-protein	5.48	5.02	0.79	
		(= 3.51 liters)		

	Calories Indirect	Calories Direct
Protein calories (0.136 grams N × 26.51) =	3.60	
Non-protein calories (3.51 liters O_2 × 4.788*) =	16.83	
	20.43	20.92

Difference, 2.5 per cent.

* Caloric value of 1 liter O_2 when non-protein R. Q. = 0.79.

[1] For slightly different values consult Benedict, F. G., and Talbot, F. B.: "The Gaseous Metabolism of Infants," Carnegie Institution of Washington, Pub. 201, 1914, p. 26.

[2] Benedict, F. G., and Fox, E. L.: Indus. and Engin. Chem., 1925, **17**, 912.

It is only a coincidence that the non-protein respiratory quotient is the same as the observed respiratory quotient.

The same method is employed in the calculations of the metabolism of man.

In a series of twenty-two different experiments with a dog Murlin and Lusk[1] obtained the following results:

	Calories
Indirect calorimetry	2244
Direct calorimetry	2230
Difference	0.6 per cent.

In fourteen of the twenty-two experiments the individual error was less than 2 per cent.

The following is a description of the principles of an Atwater-Rosa respiration calorimeter with the improvements added by Benedict,[2] Williams,[3] and others, which has been adapted for the use of patients in Bellevue Hospital:[4]

PRINCIPLE OF THE ATWATER-ROSA-BENEDICT RESPIRATION CALORIMETER[5]

The apparatus is divided into two functional parts, one for measuring the gaseous exchange, the other for measuring the heat production of the subject. A schematic presentation is here given (Fig. 3).

The Gas Analysis.—The inner lining of the apparatus presents an air-tight copper box having a capacity of 1123 liters. One end of the box, through which the patient lying on the bed is admitted, may be closed with a glass plate by means of wax. The air within the box is purified by drawing it out of an opening in the box through a rubber tube and forcing it by means of a rotary blower through a system of *absorbers*, whence it returns again to the box by another rubber tube. It passes (see diagram) first through sulphuric acid (1), which removes the water, then through moist soda lime (2), which removes the carbon dioxid, and next through sulphuric acid (3), which absorbs the moisture taken from the soda lime. If the bottles be previously weighed, the gain in weight of 1 represents water absorbed, and the gain in weight of 2 plus 3 equals the carbon dioxid absorbed. By this method the water and carbon dioxid produced by a man are taken from the air, while oxygen within the chamber is being absorbed by the man himself. This causes a diminution in the volume of the contents of the box. In order to replace the oxygen used, oxygen is automatically fed into the system from an oxygen cylinder which may be weighed before and after the period. The automatic feeding of oxygen into the box is accomplished by means of a spirometer whose interior is connected with the interior of the calorimeter chamber. As the volume of the air in the box decreases, the spirometer falls until a certain point is reached, at which an electric contact releases a clamp, which allows oxygen from the oxygen cylinder to enter the box, causing the spirometer to rise, break its electric contact, and clamp off

[1] Murlin, J. R., and Lusk, G.: J. Biol. Chem., 1915, **22**, 17.

[2] Benedict, F. G., and Carpenter, T. M.: Carnegie Institution of Washington, Pub. 123, 1910.

[3] Williams, H. B.: J. Biol. Chem., 1912, **12**, 317.

[4] Riche, J. A., and Soderstrom, G. F.: Arch. Int. Med., 1915, **15**, 805.

[5] Lusk, G.: *Ibid.*, p. 793.

the oxygen supply. So sensitive is the spirometer to the movement of the patient that a device called a "work adder" has been attached to it, which records the subject's movements.

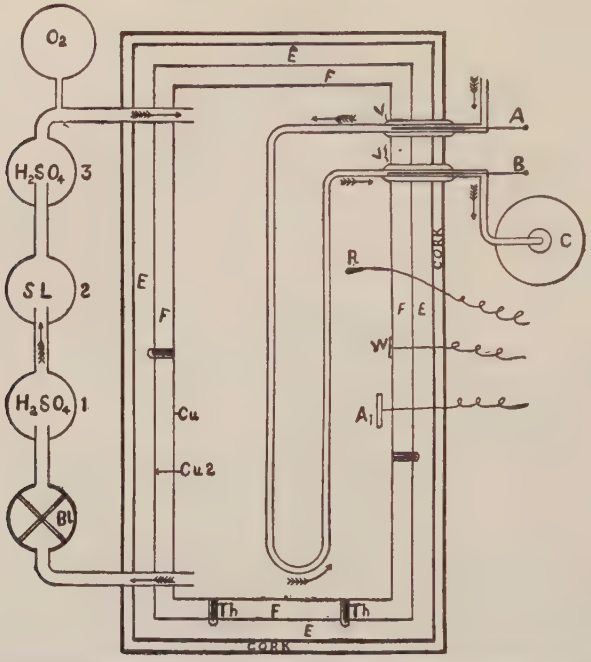


Fig. 3.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter.

Ventilating System:

O_2, Oxygen introduced as consumed by subject.

3, H_2SO_4 to catch moisture given off by soda lime.

2, Soda lime to remove CO_2.

1, H_2SO_4 to remove moisture given off by patient.

Bl, Blower to keep air in circulation.

Indirect Calorimetry:

Increase in weight of H_2SO_4 (1) = water elimination of subject.

Increase in weight of soda lime (2) + increase in weight of H_2SO_4 (3) = CO_2 elimination.

Decrease in weight of oxygen tank = oxygen consumption of subject.

Heat-absorbing System:

A, Thermometer to record temperature of ingoing water.

B, Thermometer to record temperature of outgoing water.

V, Vacuum jacket.

C, Tank for weighing water which has passed through calorimeter each hour.

W, Thermometer for measuring temperature of wall.

A_1, Thermometer for measuring temperature of the air.

R, Rectal thermometer for measuring temperature of subject.

Direct Calorimetry:

Average difference of A and B × liters of water + (gm. water eliminated × 0.586) ± (change in temperature of wall × hydrothermal equivalent of box) ± (change of temperature of body × hydrothermal equivalent of body) = total calories produced.

Th, thermocouple; Cu, inner copper wall; Cu_2, outer copper wall; E, F, dead air-spaces.

At the beginning of an hourly period of experimentation an observer at the table calls "time." At this instant the rotary blower is stopped, the air current switched so as to pass through a new set of weighed absorbers, and then the rotary blower is started again. At the word "time" an operator also turns a pet-cock which cuts off the respira-

tory chamber from the spirometer cylinder, which is then filled, always to a given point, with oxygen from the oxygen cylinder. The pet-cock is now opened and a freshly weighed oxygen cylinder is placed in the position of the other, which is removed. Repeating these procedures an hour later, one may determine by difference in weight the gain of water and carbon dioxid by the absorbers and the loss of oxygen by the cylinder. The figures are subject to corrections due to (1) gain or loss of water or carbon dioxid content in the box itself during the period, which gain or loss must be added to or subtracted from the increase in weight of the absorber system. This gain or loss of water and carbon dioxid in the box also affects the volume of the air in the box and, therefore, the quantity of oxygen admitted, as do, in addition (2), a change in temperature within the box and (3) a change in barometric pressure. These corrections must be made in order to determine whether oxygen is to be added or subtracted from the quantity which has been furnished from the oxygen cylinder. The result gives the quantity of oxygen which the man has absorbed. It is apparent that all the errors of determination fall on the oxygen, and yet the exactness of the method is witnessed by the close approximation in alcohol check experiments of the theoretic and actual values for oxygen consumed.

If a person in the calorimeter moves even the arm during the critical moments just before "time" is called, the increased local heating of the air may cause the spirometer to rise to a considerable height, of which the air thermometers inside the box fail to make compensatory record, and the oxygen determination will be too low in that hour and too high in the next.

Analysis of the air in the interior of the chamber is made just before the beginning of each hour by passing 10 liters of air from the box through three U tubes containing, respectively, sulphuric acid, soda lime, and sulphuric acid, then through a Bohr gas-meter, and back into the box again. This is called the "residual analysis."

Under the conditions present in the respiration apparatus carbon dioxid is measured with the greatest ease and accuracy. Oxygen is also measured with accuracy if the person within the box lies perfectly quiet for ten minutes before the end of the period, whereas water production is the least accurate of all the determinations on account of the varying hygroscopic condition of the walls, bedding, and other surfaces within the closed spaces of the apparatus.

The Measurement of Heat Produced.—Roughly speaking, one-quarter of the heat eliminated by a man is present in the water vapor which is absorbed by the first sulphuric acid bottle on the absorber table. At 20° C. 0.586 calorie is contained as latent heat in 1 gram of vaporized water.

The rest of the heat loss takes place by radiation and conduction. It is this heat which is measured by the calorimeter itself. The mechanism of the calorimeter is essentially twofold. In the first place, there is no heat loss through the walls of the apparatus, and, secondly, the heat produced by a man within is removed from the chamber by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. If the walls allowed no heat to pass, it is obvious that without the cooling effect of the water-pipes the temperature of the air in the box would soon attain the temperature of the human body instead of being about 23° C., at which it is usually held. The apparatus is therefore a constant-temperature, water-cooled calorimeter. It is evident that if no heat is allowed to pass through the walls of the calorimeter, then the heat produced within the chamber will be removed in the current of cold water flowing through the heat-absorbing pipes inside the chamber of the apparatus. If the temperatures of the ingoing and of the outgoing water are known and the quantity of water which has passed through the heat-absorber during an hour is measured, the quantity of heat carried away in the current of water can be accurately

determined. For example, if the difference between the temperature of the ingoing and outgoing water is 2.50 degrees, and 20 liters of water have passed through the heat absorber in one hour, then 50 calories of heat have been carried away from the apparatus during the period. If the temperature of the walls within the apparatus has undergone a change this value is subject to corrections, but otherwise the total heat elimination of the person is measured by the 50 calories so determined plus the heat value of water vaporized during the hour.

To obtain an even flow of water through the heat-absorber the water is supplied from a constant-level tank placed above the calorimeter. To obtain ingoing water of an even temperature Williams passed the previously ice-cooled water current through a Gouy temperature regulator and then through a current regulator designed by himself. These improvements allow the ingoing water to enter the calorimeter at a temperature which may not vary more than 0.02° C. during hours of experimentation and, for the first time, permit the exact measurement of small quantities of heat in this type of apparatus. The temperatures of the ingoing and outgoing water are taken every four minutes by electric resistance thermometers and are read in connection with a galvanometer and Kohlrausch bridge on an observer's table. The quantity of the water-flow is determined by weighing; the water is diverted at the call of "time," so that the exact quantity for the hour is collected in a previously weighed receptacle.

Having learned how the heat produced within the apparatus is carried away, the problem of how to prevent loss of heat through the walls of the chamber remains to be discussed. This was accomplished through a device introduced by Rosa. The calorimeter is constructed of three walls, an inner copper wall which has already been described as the lining of the respiration chamber, an outer copper wall separated from the inner wall by a space of dead air, and an insulating wall (made of two layers of "compo-board," the space between them being filled with cork), which insulating wall is separated from the outer copper wall by a second space containing dead air. It is obvious that if the inner and outer copper walls of the calorimeter have the same temperature there will be no exchange of heat between them. Therefore, to prevent a gain or loss of heat by the inner wall, it is necessary to maintain the outer wall always at exactly the same temperature as the inner wall, under which circumstances the latter cannot gain or lose heat to its neighbor.

In order to detect differences in temperature between the outer and inner walls Rosa arranged thermo-couples in series between the two walls. In this fashion the top, sides, and bottom of the box are successively tested every four minutes by an operator at the observer's table to determine whether there is any difference in temperature between the outer and inner walls. If the outer wall is found to have a different temperature from the inner wall, its temperature is brought to that of the inner wall by the following device: A cooling current of water runs through pipes between the insulating and outer copper wall, and in this same space, along the line of the pipes, run "Therlo" resistance wires carrying an electric current for the warming of this interspace (see Fig. 4). By varying the intensity of the electric currents which severally supply the spaces to top, sides and bottom, the temperature of these spaces can be so controlled as to heat or cool the outer copper wall and maintain it at exactly the same temperature as the inner copper wall. This is the effective system which prevents a loss or gain of heat through the wall of the calorimeter.

Resistance thermometers are attached to the inner walls of the calorimeter, and if the temperature of the walls rises or falls between the beginning and end of the experiment, a correction must be made. It has been found that 19 calories are absorbed by the Sage calorimeter when the inner wall rises 1 degree. Conversely, 19 calories are given up by a fall of 1 degree. This is the *hydrothermal equivalent* of the box.

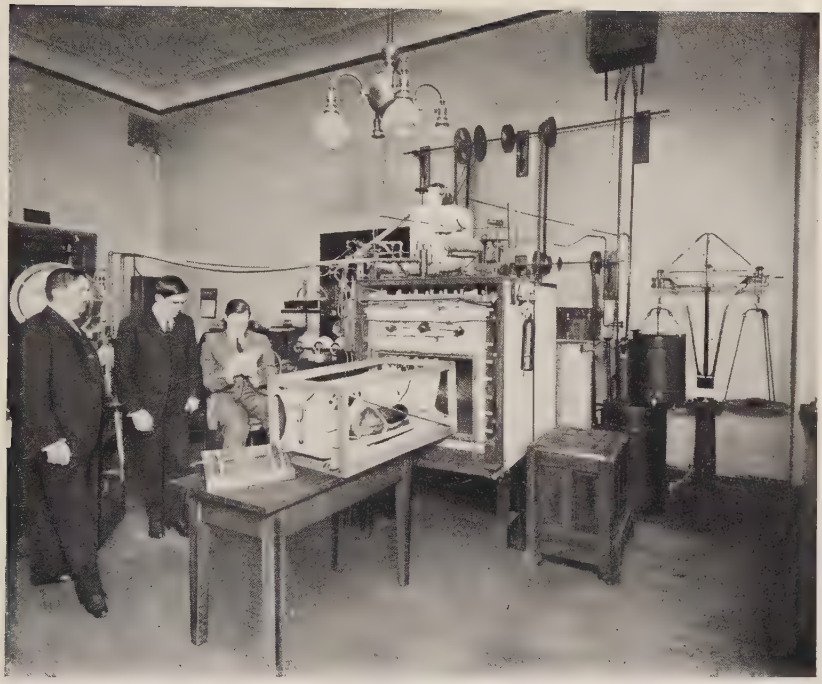


Fig. 4.—This figure shows a small respiration calorimeter built by H. B. Williams for the Physiological Laboratory, Cornell University Medical College, New York City. A dog, wearing a bandage which holds a rectal thermometer in place, is shown lying on a cot suspended from a frame which may at any time be slid into the open chamber of the calorimeter. This accomplished, the front is then sealed. The animal respires within the chamber; the water and carbonic acid which he eliminates are removed by circulating the air through absorbing chemicals, and fresh oxygen is admitted automatically to replace the oxygen absorbed by the animal. The heat produced by the dog is removed by a current of water flowing through a system of pipes within the calorimeter.

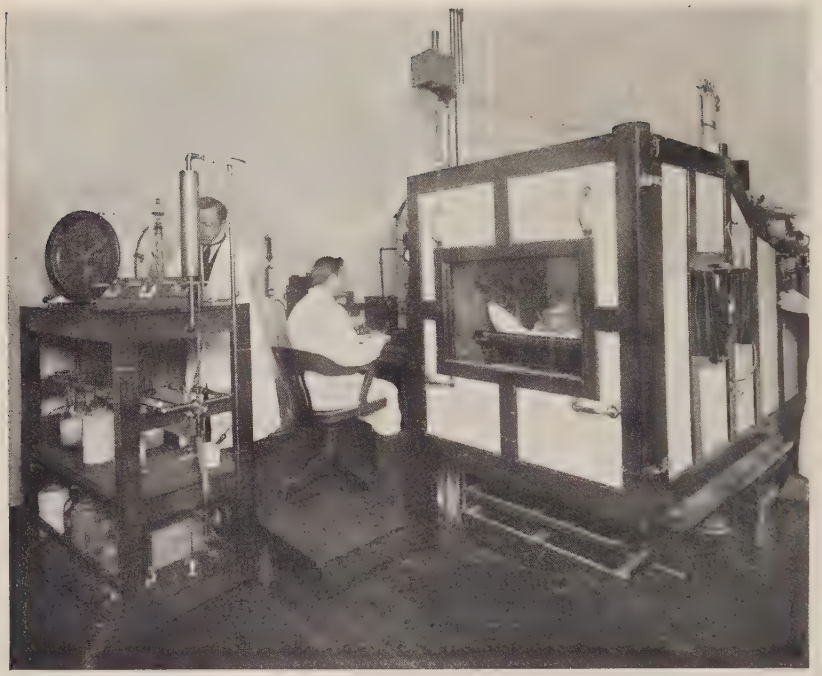


Fig. 5.—Showing the respiration calorimeter of the Russell Sage Institute of Pathology which is affiliated with the Second (Cornell) Medical Division of Bellevue Hospital, New York City. From left to right, observer 3 is at the "absorber table;" the residual U tubes and the 10-liter meter are on top; the "absorbers" of CO_2 and H_2O are on the middle shelf, and the "blower" on the lower shelf. Observer 1 is at the electric control table. Observer 2 is filling the spirometer with his right hand from an oxygen cylinder he is touching with his left.

The temperature of the air entering the box from the absorbing table is always heated to exactly the same temperature as the air leaving the box.

Finally, an electric resistance thermometer inserted 10 or 12 cm. into the rectum of the person in the calorimeter gives information regarding the retention or loss of heat in his organism. The specific heat of a man is assumed to be 0.83, that is to say, 0.83 calorie raises 1 kilogram 1 degree. If, therefore, the body temperature of a man weighing 70 kilograms rises or falls 1 degree, the quantity of heat lost or gained by the body will be 70×0.83, or 58.1 calories. This is on the assumption that the rise of body temperature is everywhere the same as takes place in the rectum, a supposition which, unfortunately, is not always true (see p. 146).

The accompanying scheme gives the details regarding the employment of the three individuals who conduct a calorimeter experiment.

It may be added that special care has been taken to make the appearance of the calorimeter attractive to the eye, and that the spirit of the small ward in connection with the calorimeter work has been such that the patients have considered themselves especially fortunate when chosen for the diversion offered by a morning's occupancy of the apparatus.

SCHEME OF EMPLOYMENT OF OBSERVERS IN A CALORIMETER EXPERIMENT

Period of Observation	Observer 1, at Electric Control Table	Observer 2, in Charge of Experiment	Observer 3, Calculator
Eight minutes before.	Brings walls into exact thermal equilibrium.	Signals subject to lie absolutely quiet.	Starts passing first 10-liter sample of residual air through U tubes.
Five minutes before.	.....	Starts kymograph record of movements of spirometer.	
Four minutes before.	.....	.....	Finishes first and starts second residual.
One-half minute before.	Takes final reading of air, walls, and rectal temperature.	Sets barometer.	Finishes second residual.
At "Time."	Presses button which diverts stream of water from weighing tank.	Shuts spirometer off from box. Fills to standard level from oxygen tank.	Stops ventilating current of air. Turns valve to pass air through newly weighed absorbers. Starts ventilating current.
Immediately after "Time."	Starts taking readings every four minutes of ingoing and outgoing water, of air, walls, rectal, and surface thermometers. Reads and adjusts temperature of top, sides, and bottom of calorimeter, of the ingoing air and water every four minutes, or oftener if necessary.	Records and sets workadder. Signals to subject that he may move. Weighs oxygen tank and connects with box again. Weighs sulphuric and soda lime bottles. Connects them up again and tests for leaks. During remainder of hour counts pulse, inspects valves for leaks, adjusts temperature of room, watches subject, etc.	Weighs water tank which has received all the water from the heat absorber during the past hour. Diverts stream of water to this tank again. Records barometer. Weighs residual. Calculates results of the hour just finished.

ADDENDUM SHOWING THE HARMONY BETWEEN THE RESULTS OF RUBNER AND OF ATWATER

Tigerstedt[1] has applied Rubner's standard values (see p. 41) to a recalculation of Atwater's calorimeter experiments and finds them to be valid. Atwater found in certain experiments with men who took a mixed diet that of an aggregate 51,000

[1] Tigerstedt, R.: Nagel's "Handbuch der Physiologie des Menschen," Braunschweig, 1909, I, p. 370.

calories were produced, and Tigerstedt's recalculation on the basis of Rubner's standard figures showed an aggregate of 51,087 calories.

In these calculations consideration was given to the fact that the number of calories used by Rubner is the amount of heat necessary to raise a liter of water from 0° to 1° C., whereas that of Atwater is for water between 20° and 21°, or 1 per cent lower. For Atwater's work Tigerstedt modifies Rubner's standards as follows:

	Calories
1 gm. protein	4.2
1 gm. fat	9.4
1 gm. carbohydrate	4.15

The components of the ingested diet were multiplied by their respective values, and from this total was deducted the estimated caloric value of the "protein," "fat," and "carbohydrate" determined by Atwater in the feces. This gave the food absorbed, and a further correction for the quantity of fat or protein gained or lost by the body gave the value of the food oxidized. Individual experiments are as follows:

	Atwater's Experiment	
	No. 25 Man at Rest	No. 34 Man at Work
Calories in the diet (actually determined) less the calories in urine and feces ± calories of fat and protein added to or withdrawn from the body	2241	3644
Calories produced by the individual, as directly measured by Atwater-Rosa calorimeter	2244	3587
Calories calculated for diet as per Rubner's "standard values" less the calories of "protein," "fat," and "carbohydrate" in the feces ± calories of fat and protein added to or withdrawn from the body	2292	3667

In this extensive series of 50 experiments upon three different normal men Atwater[1] found that, of the content of the ordinary mixed diet ingested, there was an average elimination in the feces of nitrogen, 9.2 per cent.; of "fat," 4.7 per cent.; of carbohydrate, 2.4 per cent.; and of total gross energy intake, 8.4 per cent. (compare with Rubner, p. 41).

[1] Atwater, O.: Ergeb. d. Physiol., 1904, **3**, Pt. 1, 540.

CHAPTER IV

STARVATION

Die Ursache der Art des Existenz ist bei jedem Teile eines lebenden Wesens im Ganzen enthalten während bei todten Massen jeder Teil sie in sich selbst trägt.—KANT.

NUTRITION may be defined as the sum of the processes concerned in the growth, maintenance, and repair of the living body as a whole or of its constituent organs.

An intelligent basis for the understanding of these processes is best acquired by a study of the organism when it is living at the expense of materials stored within itself, as it does in starvation.

Starvation or hunger is the deprivation of an organism of any or all the elements necessary to its nutrition. Thus when carbohydrates and fats only are eaten, protein hunger ensues. If the body is deprived of water or of calcium, thirst or calcium hunger, as the case may be, follows. Complete starvation occurs when all the required elements are inadequate. A fasting dog to which no food or drink is offered does not undergo starvation in this sense, for the metabolized tissue furnishes enough water for the urine and respiration. There is also no water hunger in a dog when meat is ingested, for the meat contains enough water to dissolve the end-products of its metabolism in the urine. Dogs and cats have no sweat-glands in the skin except in the pads of their feet. They therefore are not so susceptible to water hunger as is man, whose body surface is constantly losing moisture.

A true picture of water hunger is presented by Straub,[1] who gave a dog dry meat powder mixed with fat. Under these circumstances water is withdrawn from the tissues to dissolve the urea formed. He found that muscles may lose 20 per cent. of their water content without pathologic manifestations, although withdrawal of water somewhat increased the protein metabolism. The experiment could not be carried to the point of death from thirst, for after a few days the food was regularly vomited, on account of the decreased flow of the digestive secretions and an altered condition of the intestinal

[1] Straub, W.: Z. f. Biol., 1899, **38**, 537.

canal. The non-absorption of the meat powder threw the body on the resources of its own tissue, and this form of starvation, as has been shown, does not constitute water hunger.

Rubner[1] finds that starving pigeons die of thirst in four to five days, while those allowed only water live twelve days. Water hunger is, therefore, more quickly fatal than starvation when water is allowed. Under the usual conditions of so-called starvation experiments water is freely allowed, so that water hunger does not enter as a factor into the following discussion.

If water be available, the organism obtains the energy necessary for its continued existence from the destruction of its own store of protein and fat. After a variable length of time the organism succumbs. Exposure to cold greatly hastens the end. What is ordinarily called death from starvation is often really death from exposure.

Boldireff[2] described rhythmic movements occurring in the empty stomach, and Cannon and Washburn[3] have called attention to the intimate association of these contractions with the pangs of hunger. The subject has been studied in detail by Carlson[4] in observations upon a boy with a gastric fistula. Twenty-four hours after a meal the stomach exhibited two types of rhythmic movements: (1) relatively feeble, but continuous contractions at the rate of three per minute, and (2) relatively strong contractions of the fundus, the true hunger-pains. The amplitude of these latter contractions shows a close correspondence with the intensity of the sense of hunger simultaneously registered. During strong contractions the knee-jerk was found to be exaggerated, indicating an increased tonus of the nervous system, and there was a great instability of vasomotor tone. Carlson suggests that this close association of the hunger-pains with the vasomotor center may be the cause of the faintness occurring in starvation. The hunger contractions and, in consequence, the hunger pangs are inhibited by: (1) the stimulation of the gustatory nerves through sweet, bitter, salt, and acid substances; (2) chewing any kind of substance, be it well or ill flavored or tasteless; (3) smoking; (4) swallowing movements. Water, coffee, tea, beer, wine, and

[1] Rubner, M.: E. v. Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, p. 53.
[2] Boldireff, W. N.: Arch. d. sc. biol., 1905, **11**, 1.
[3] Cannon, W. B., and Washburn, A. L.: Am. J. Physiol., 1911–12, **29**, 441.
[4] Carlson, A. J.: *Ibid.*, 1912–13, **31**, 151.

brandy when taken into the stomach inhibit the movements and relieve the sense of hunger, though water is least effective in this regard.

Another man, described by Carlson,[1] underwent two fasts, one of 10, the other of 15 days' duration, during which the hunger contractions were strong and persistent. There was general muscular and mental depression and increased psychical irritability. There was a continuous secretion of gastric juice, epigastric distress, and a bad taste in the mouth. The dominant element in consciousness was of food and drink.

RECORD FASTS

Succi fasted several times for thirty days. Dr. Tanner, an American physician, for forty days; and Merlatti, in Paris, for fifty days. Succi took laudanum in considerable quantity to stay the pain in his stomach, while Merlatti took only water.[2] The effect of fasting on the spirits of the faster varies with the individual. Usually there is a loss of buoyancy of spirit, a decreased desire to work, and a decrease in the actual power of working. Succi, however, was capable of considerable exertion, such as walking and riding, without ill effects. A dog does not manifest the same depression as is seen in man. Dogs may be starved several days before they are run in a hunt. One of the longest fasts on record is that of Kumagawa's[3] dog, which died on the ninety-eighth day. This dog was reduced in weight from 17 to 5.96 kilograms, a loss of 65 per cent.

A yet longer fast has been reported by Hawk,[4] in which a dog fasted from February 6th to June 2d, a period of 117 days, 700 grams of water having been administered daily. The dog remained in "good spirits" during the whole fast, although its weight fell from 26.3 to 9.76 kilograms. There was no indication of a "premortal rise" in the nitrogen elimination in the urine. During the first four days of fasting the average nitrogen elimination in the urine was 6.23 grams or 0.23 gram per kilogram of body weight, and during the last four days it averaged 2.44 grams or 0.23 gram per kilogram. The dog then passed the summer upon a Kansas farm, fully regained his former weight, and in the autumn was reported to be in better physical condition than at the commencement of his fast. A second

[1] Carlson, A. J.: Am. J. Physiol., 1917–18, **45**, 120.
[2] Luciani, L.: "Das Hungern," Hamburg and Leipzig, 1890, p. 28.
[3] Kumagawa, M., and Miura, R.: Arch. Physiol., 1898, p. 431.
[4] Howe, P. E., Mattill, H. A., and Hawk, P. B.: J. Biol. Chem., 1912, **11**, 103.

or "repeated fast" was then initiated which lasted 104 days with no harmful results.

The day to day history of the starving organism must now be considered.

INFLUENCES AFFECTING PROTEIN METABOLISM

In the first days the amount of protein metabolized depends upon the two factors, the glycogen content of the individual and the quantity of protein ingested before the starvation period. The influence of the first factor was shown by Prausnitz.[1] Fifteen individuals (mostly medical students who were taking a course of instruction in the laboratory) fasted for sixty hours. The first day's urine was collected beginning after twelve hours of fasting. The second day's urine contained in 12 cases more nitrogen than that of the first day of starvation. The lower protein destruction on the first starvation day must have been due to the continued use of sugar from the glycogen supply. It is known that the combustion of sugar considerably reduces the protein metabolism, so the second day and not the first of starvation should be taken as the basis of the fasting protein metabolism.

This influence of glycogen metabolism on that of protein during the first and second days of fasting is beautifully shown in experiments by Benedict[2] (see also p. 98).

INFLUENCE OF GLYCOGEN METABOLISM ON THAT OF PROTEIN IN FASTING. WEIGHTS IN GRAMS

Individual	First Day			Second Day		
	Glycogen Metabolized		N Eliminated	Glycogen Metabolized		N Eliminated
	Total	Per Kg.		Total	Per Kg.	
S. A. B.	181.6	3.15	5.84	29.7	0.52	11.04
S. A. B.	135.3	2.31	10.29	18.1	0.31	11.97
S. A. B.	64.9	1.09	12.24	23.1	0.39	12.45
H. C. K.	165.6	2.33	9.39	44.7	0.64	14.36
H. R. D.	32.8	0.59	13.25	41.6	0.76	13.53

It is evident that where there is an abundant glycogen reserve the protein metabolism is reduced by the oxidation of carbohydrates, but where there is little glycogen to draw upon the protein metabolism is high even on the first day of starvation.

[1] Prausnitz, W.: Z. f. Biol., 1892, **29**, 151.

[2] Benedict, F. G.: "The Influence of Inanition on Metabolism," Carnegie Institution of Washington, Bull. 77, 1907.

The second factor, or the influence of the previous meat ingestion, is especially dominant in dogs. (For effect on man see p. 358.) Voit[1] fed a dog weighing 35 kilograms with different quantities of meat and noticed the effect on urea elimination during subsequent starvation. The results were as follows:

INFLUENCE OF PREVIOUS DIET ON UREA ELIMINATION IN STARVATION

	Grams of Urea Excreted during Starvation Following Various Diets				
	Meat, 2500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread
Last food day	180.8	130.0	110.8	110.8	24.7
1st fasting day	60.1	37.5	29.7	26.5	19.6
2d " "	24.9	23.3	18.2	18.6	15.6
3d " "	19.1	16.7	17.5	15.7	14.9
4th " "	17.3	14.8	14.9	14.9	13.2
5th " "	12.3	12.6	14.2	14.8	12.7
6th " "	13.3	12.8	13.0	12.8	13.0
7th " "	12.5	12.0	12.1	12.9	
8th " "	10.1	....	12.9	12.1	
9th " "	....	....	....	11.9	
10th " "	....	....	....	11.4	

It is evident from this that on the sixth day of starvation the urea elimination was the same in all cases, or about 13 grams of urea per day. Voit deducted the 12 grams from what he had found for the first days and obtained the grams of urea which were derived from the previous food, as follows:

UREA ELIMINATION IN GMS. IN STARVATION ATTRIBUTABLE TO PREVIOUS DIET

	Meat, 1500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread
(Last food day)	(168.8)	(118.0)	(98.8)	(98.8)	(12.7)
1st fasting day	48.1	25.5	17.7	14.5	7.6
2d " "	12.9	11.3	6.2	6.6	3.6
3d " "	7.1	4.7	5.5	3.7	2.9
4th " "	5.3	2.8	2.9	2.9	1.2
5th " "	0.3	0.6	2.2	2.8	0.7

The amount of extra protein metabolism is seen from the above to be directly dependent on the previous feeding, a common level being reached in all cases on the fifth day of fasting.

These experiments led Voit to differentiate between "circulating protein," which could be absorbed, carried to the tissues, and burned,

[1] Voit, C.: Z. f. Biol., 1866, **2**, 307.

and "organized protein," the more resistant living protein of the tissues themselves. Voit[1] stated that in metabolism the lifeless protein furnished to the cells by the blood was used in preference to the living organized tissue protein. He quoted Landois' experiments, which show that after producing an artificial plethora through injection of blood, the serum proteins are readily burned and their nitrogen eliminated in the urine, while the red blood-cells containing the organized protein are only slowly destroyed. If serum alone be transfused, its protein is rapidly destroyed[2] (see p. 194).

Even in starvation there is evidence of "circulating protein" as food for the tissues. Thus Miescher showed that the salmon, after entering the Rhine from the sea, virtually starves. Yet the genital organs of both male and female develop greatly, this being at the expense of the muscles, which may lose 55 per cent. of their weight. This protein must have been carried to the various parts of the body in the circulating blood-stream. Miescher finds no indication of any destruction of muscle-fibers in this process of emaciation (see p. 310). It is interesting in this connection to note that A. R. Mandel[3] has been able at a pressure of 300 to 350 atmospheres acting on lean meat seventy-two hours old to press out a fluid containing 44 per cent. of the protein present in the fibers, and this without visible change from the normal histologic appearance of the muscle.

THE COMPOSITION OF PROTEIN

It seemed quite possible that in ordinary starvation protein from muscle and other tissues passed to the blood and was carried to all the organs as circulating protein for the nutrition of their cells.

The great work of Kossel, Hofmeister, and Emil Fischer has taught that the essential composition of protein is a structure formed of chains of amino-acids. It was Kossel[4] who forecast the polypeptid nature of the protein molecule. Hofmeister,[5] in a celebrated address at Carlsbad in 1902, marshalled the small amount of evidence then available and convincingly demonstrated that the union of amino-acids was the essential structural factor in the protein molecule. At

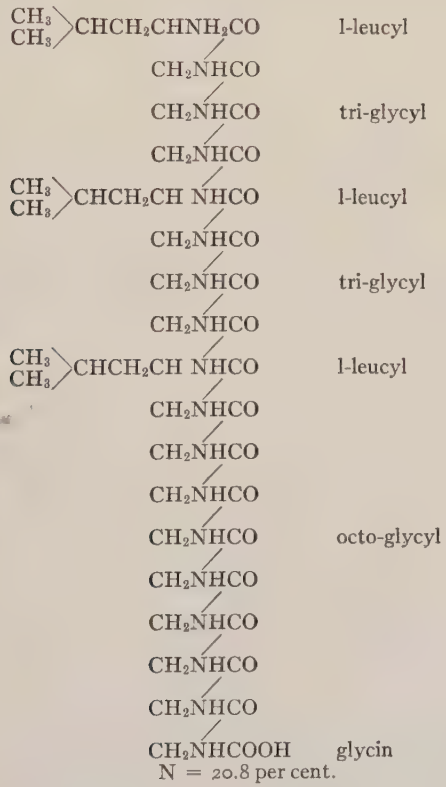
[1] Voit, C.: L. Hermann's "Physiologie," Leipzig, 1881, **6,** Pt. 1, p. 300.
[2] Forster, J.: Z. f. Biol., 1875, **11,** 496.
[3] Mandel, A. R.: Unpublished work from the Munich Clinic of Prof. Fr. Müller.
[4] Kossel, A.: Z. physiol. Chem., 1898, **25,** 174; Ber. d. D. chem. Ges., 1901, **34,** 3214.
[5] Hofmeister, F.: Verhandl. d. Naturforscherversam., Carlsbad, 1902, p. 621; Ergeb. d. Physiol., 1902, **1,** 795.

the time of this address Fischer[1] was at work upon the synthetic production of polypeptids. In 1906 Fischer[2] wrote: "Strong support for this view is afforded by the striking similarity of the artificial polypeptids with the peptones, especially as regards their behavior with pancreatic juice, and also because of the direct preparation from silk of glycyl-d-alanin."

Fischer has constructed artificial *peptids*, bodies in which two or more amino-acids are united together. For example, glycyl-glycin is formed by the union of two molecules of glycin with the loss of water, as follows:

$$\underset{\text{Glycin}}{H_2NCH_2COOH} \quad \underset{\text{Glycin}}{H_2NCH_2COOH} \quad -H_2O \quad = \quad \underset{\text{Glycyl-glycin}}{H_2NCH_2CO\text{-}HNCH_2COOH}$$

Fischer has hung together eighteen of these radicles in an octodecapeptid containing four leucin and fourteen glycin molecules and being l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octoglycyl-glycin.



N = 20.8 per cent.

[1] Fischer, E., and Fourneau, E.: Ber. d. d. chem. Ges., 1901, **34**, 2868.
[2] Fischer, E.: *Ibid.*, 1906, **39**, 530.

This forms a body akin to pepton. The high molecular complexes called proteins, which constitute the basis of our being, are, after all, separable into simple chemical compounds. In the larger molecule these amino-acids are chained together, even as in structural framework various iron beams are riveted together. Digestive proteolysis or internal metabolism rends the higher structure of the molecule and leaves its individual supports, the amino-acids, open for further disintegration.

The various proteins differ from one another in the relative quantity of the different amino-acids which they contain, and also undoubtedly in the manner of chemical linkage of those acids. Thus Abderhalden has called attention to the fact that if the seventeen different chemical units be joined together in different ways, 350,000,000 times 1,000,000 different combinations are possible even though only a single representative of each unit is used. In this manner the amino-acids may form combinations the possible multiplicity of which recalls the number of words in the dictionary formed from the letters of the alphabet.

The table on page 83, except for one column (recalculated composition of ox muscle), has been taken from Plimmer.[1] This summary of results is based upon analytical data gleaned from about 300 different scientific papers which are separately quoted by Plimmer in his book on the proteins.[2] This demonstrates the immensity of the background of biological literature. The names of Kossel, Osborne, Abderhalden, and Dakin suggest to the memory notable contributions in this field.

Concerning the crystalline vegetable proteins which he has investigated Osborne[3] writes: "It is possible to establish a constancy of properties and ultimate composition between successive fractional precipitations which give no reason for believing the substance to be a mixture of two or more individuals. On chemical grounds there is no more reason for dividing the proteins into two groups of animal and vegetable proteins than there is for making a similar distinction between the carbohydrates. Of twenty-three seed proteins which have been hydrolized, all have yielded leucin, prolin, phenylalanin,

[1] Plimmer, R. H. A.: "Practical Organic and Bio-Chemistry," new edition, London, New York, etc., 1926, p. 367.
[2] Plimmer, R. H. A.: "Chemical Constitution of the Proteins," 3d ed., London, New York, etc., 1917.
[3] Osborne, T. B.: Science, 1908, **28**, 417.

aspartic acid, glutamic acid, tyrosin, histidin, arginin, and ammonia. Glycin, lysin, and tryptophan are the only amino-acids which have been proved lacking in any one of these proteins."

PERCENTAGE AMOUNTS OF AMINO-ACIDS DERIVED FROM VARIOUS PROTEINS

	Sturin	Ox Muscle Protein	Lactalbumin	Gelatin	Caseinogen	Wheat Gliadin	Wheat Glutenin	Maize Zein	Silk Fibroin	Globin of Hemoglobin	Ox Muscle[1] Protein (Recalculated)
Glycin	....	2.1	0	25.5	0	0	0.9	0	36.0	....	4.0
Alanin	....	3.7	2.5	8.7	1.5	2.0	4.7	9.8	21.0	4.2	8.1
Valin	....	0.8	0.9	0	7.2	3.4	0.2	1.9	....	....	2.0
Leucin	....	11.7	19.4	7.1	9.4	6.6	6.0	25.0	1.5	29.0	14.3
Isoleucin	....	....	....	0							
Aspartic acid	....	4.5	1.0	3.4	4.1	0.6	0.9	1.8	+	4.4	10.6
Glutamic acid	....	15.5	10.1	5.8	21.6	43.7	23.4	31.3	0	1.7	22.3
Serin	....	....	....	0.4	0.5	0.2	0.7	1.0	1.6	0.6	
Hydroxyglutamic acid	....	....	....	0	10.5	....	....	2.5			
Prolin	....	5.8	4.0	9.5	8.0	13.2	4.2	9.0	+	2.3	8.0
Hydroxyprolin	....	....	....	14.1	0.3	....	....	....	....	1.0	
Phenylalanin	....	3.2	2.4	1.4	3.2	2.4	2.0	7.6	1.5	4.2	4.5
Tyrosin	....	2.2	0.9	0.01	4.5	1.2	4.3	5.2	10.5	1.3	4.4
Tryptophan	....	+	....	0	1.7	1.0	+	0	....	+	+
Lysin	12.0	7.6	9.2	5.9	6.0	0.2	1.9	0	+	4.3	7.6
Arginin	58.2	7.5	3.2	8.2	3.8	3.2	4.7	1.8	1.0	5.4	11.5
Histidin	12.9	1.8	2.1	0.9	2.5	0.6	1.8	0.8	+	11.0	4.5
Cystin	....	....	....	?	....	0.5	0.02	....	....	0.3	
Ammonia	....	1.1	1.3	0.4	1.6	5.2	4.0	3.6	....	....	1.1
Total	83.1	67.5	57.0	91.31	86.4	84.0	59.72	101.3	73.1	69.7	102.9

[1] Osborne, T. B., and Jones, D. B.: Am. J. Physiol., 1909, **24**, 437, modified by the findings of Osborne and Jones, *Ibid.*, 1910, **26**, 305.

Osborne and Abderhalden were agreed that the chemical constituents of protein were probably all known, and that the usual deficit found on their analysis is due to the inadequacy of the methods employed. Thus Osborne and Jones found that they recovered varying percentages of different amino-acids when a mixture of known quantities was analyzed. If one computes their analysis of ox muscle protein on the basis of analytic losses similar to those found when the mixture of known quantities of amino-acids was analyzed, one obtains nearly 103 per cent. of the value of the original ox protein. This value includes the water added by hydrolysis in the break-up of the molecule.

A new amino-acid β-hydroxyglutamic acid has recently been added to the list by Dakin (see p. 243).

Osborne finds that the quantity of ammonia liberated in hydrolysis bears a constant relation to the amount of glutamic and aspartic acids recovered. He concludes that one of the carboxyl groups

(COOH) exists as an amid $(CONH)_2$, and that in reality glutamin and asparagin are present in the molecule, and become the sources of ammonia when the molecule is broken.

THE INTERPLAY BETWEEN PROTEIN AND AMINO-ACIDS

The physiology of protein metabolism has become in late years the physiology of the amino-acids. When once so regarded, the problem is one of the study of the behavior within the body of chemical entities which can be prepared in pure crystalline form and the formulæ of which are definitely known. The fate of these individual amino-acids will be considered at another time (see p. 222). It is sufficient to state here that the cleavage of protein into amino-acids through digestion hydrolysis is accomplished without the liberation of an appreciable quantity of heat,[1] that the resulting amino-acids are absorbed directly into the blood-stream, and that in so far as they are reconstructed into new protein within the organism the process takes place without any measurable thermodynamic reaction (see p. 297). Since the protein content of blood-plasma is nearly the same in fasting as after large ingestion of meat, it is evident that the storage of such ingested protein must be effected elsewhere than in the blood.

That the diet does not appreciably change the composition of the fat-free muscle substance is indicated by the constancy of the N:C ratios in the muscles of adult dogs. Our information comes from Stockhausen[2] and from Diesselhorst.[3]

Diet	N:C in Dog Muscle
(a) Little meat	1:3.261
(b) Meat in quantity	1:3.261
(a) Rice	1:3.22
(b) Meat in quantity	1:3.23
(a) Fasting	1:3.188
(b) Mixed diet	1:3.185

A preliminary survey of the more recently discovered information regarding the interplay between the proteins and the amino-acids of the organism may be of service at this juncture. The absorption of amino-acids by the blood was first indicated by the work of Howell,[4] who dialyzed dog's blood both before and after giving meat, and in

[1] Hári, P.: Pflüger's Arch. gesam. Physiol.," 1906, **115**, 11.
[2] Stockhausen, J.: Dissertation, Königsberg, 1909.
[3] Diesselhorst, G.: Pflüger's Arch. gesam. Physiol., 1915, **160**, 522.
[4] Howell, W. H.: Am. J. Physiol.," 1906, **17**, 273.

the latter instance recovered more material on adding naphthyl-sulpho-chlorid to the diffusate than in the former. The precipitate, however, was an oil and its quantity could not be measured accurately. Folin and Denis[1] introduced glycin or alanin into the small intestines of cats, and on analyzing the blood and muscle tissue noticed a large increase in the quantity of "residual nitrogen" which was obtained by subtracting "urea nitrogen" from "total non-protein nitrogen." The increase was so great that it could only have been caused by the influx of the amino-acids themselves. An hour after the introduction of the amino-acids urea appeared in increased quantity in the blood. Their results indicate that absorbed amino-acids circulate in the blood, are retained in the muscle tissue, and that after an hour urea rises in the blood in response to the increased production of urea in the tissues. They found no increase in the quantity of urea or of ammonia in the blood of the portal vein after introducing glycin or alanin into a loop of the intestine, and by this experiment demonstrated that the amino-acids were absorbed unchanged without deamination, which would have involved ammonia or urea production.

Van Slyke and Meyer[2] were able to determine directly the quantity of amino-acids in the blood. Thus the absorption of 12 grams of glycin from the intestine of a dog caused an increase in the amino-acid content of the blood from 3.9 to 6.3 milligrams per 100 c.c. of blood volume. After giving 1000 grams of meat to a dog the amino-acid content of the blood doubled or more than doubled in a mesenteric vein, and the urea content also increased. There was almost as great an increase in the amino-acid content of the femoral vein as in the mesenteric, and therefore Van Slyke concludes that amino-acids are not largely retained by the liver.

Van Slyke and Meyer[3] have confirmed the work of Folin and Denis in showing that the tissues absorb amino-acids with great avidity. The normal concentration of amino-acids in the tissues was found to be five to ten times that in the blood. Maximal figures are given as 80 milligrams per 100 grams of muscle, and 150 milligrams per 100 grams of liver. In one experiment the introduction into the vein of a dog of amino-acids derived from casein and containing 4.06 grams of nitrogen resulted after half an hour in an

[1] Folin, O., and Denis, W.: J. Biol. Chem., 1912, **12**, 141, and previous papers.
[2] Van Slyke, D. D., and Meyer, G. M.: *Ibid.*, 1912, **12**, 399.
[3] *Ibid.*, 1913–14, **16**, 197.

increase of amino-acids in the blood from 3.9 to 45.4 milligrams per 100 grams. This quantity would account for 5 per cent. of the total amount injected, and since 11 per cent. was eliminated in the urine it appears that the remainder or 3.41 grams of N must have been absorbed by the tissues.

Finally, it was shown by Van Slyke and Meyer[1] and independently by Wishart[2] that although the ingestion of meat in large quantity increases the amino-acid content of the blood, it does not increase that of muscle tissue. It is therefore probable that when nitrogen is retained in the organism it is not to an appreciable extent stored as digestion products, but rather in the form of protein (see p. 203). Such amino-acids as are not so synthesized are, therefore, destroyed as rapidly as they accumulate.

Van Slyke and Meyer[3] conclude that absorbed amino-acids disappear rapidly from the liver, although their concentration in the muscle suffers no appreciable fall. The urea concentration in the blood increases. The liver desaturates itself and in this way metabolizes superfluous protein.

Bollman, Mann, and Magath[4] have shown that, following the extirpation of the liver in dogs, there is no formation of urea. If the kidneys also be removed there is no accumulation of urea in the blood or tissues. The formation of urea must therefore be exclusively a function of the liver. This settles a long disputed question. After hepatectomy the amino-acid content of the blood increases, and if glycin be injected intravenously there is no evidence of its conversion into urea.

The first actual isolation of an amino-acid from blood was reported by Abel[5] at the International Physiological Congress held at Groningen in the summer of 1913. Alanin was found in considerable amount in a diffusate formed by dialyzing the blood during its continuous passage from an artery of a living animal through a system of tubes made of celloidin immersed in a saline solution, the blood then returning to the animal by a vein. This method of *vividiffusion* yields alanin in crystalline form. Histidin and creatinin may be

[1] Van Slyke, D. D., and Meyer, G. M.: J. Biol. Chem., 1913–14, **16**, 231.
[2] Wishart, M. B.: *Ibid.*, 1915, **20**, 535.
[3] Van Slyke, D. D., and Meyer, G. M.: *Ibid.*, 1913–14, **16**, 231.
[4] Bollman, J. L., Mann, F. C., and Magath, T. B.: Am. J. Physiol., 1924, **69**, 371, 393.
[5] Abel, J. J., Rowntree, L. G., and Turner, B. B.: J. Pharm. and Exper. Therap., 1913–14, **5**, 611; also, Trans. Am. Physicians, 1913.

determined by color reactions. Sugar, urea, ammonia, β-oxybutyric acid, and lactic acid also diffuse from the blood in marked amounts.

Abderhalden[1] worked with 50 and 100 liters of blood-serum and reports the presence of ten different amino-acids. Abel[2] calls attention to the fact that secondary changes which may conceivably take place in shed and coagulated blood play no part in his method of vividiffusion, which separates diffusible substances from the circulating blood of living animals.

Van Slyke and Meyer[3] report that free amino-acids do not disappear from the tissues on fasting, but, if anything, they tend to increase there.

These facts are interpretative of conditions in fasting. That amino-acids are produced in fasting is demonstrated in the cited instance of the salmon in which the protein of the genital organs increases at the expense of muscle protein. Thus Kossel[4] estimates that a salmon weighing 9 kilograms deposits at breeding time in its testicles 27 grams of salmin containing 22.8 grams of arginin. Kossel calculates that metabolism of muscle protein during this time yields ample arginin to form the new salmin.

Other evidence of the constant production of amino-acids in the tissues in fasting is offered by the experiments of Turner, Marshall, and Lamson.[5] In these important investigations one-third the blood of a dog was withdrawn, the blood corpuscles were washed with normal saline, and then the washed corpuscles were returned to the body. This process is called by Abel *plasmapharesis*. Three such bleedings, with the return of the corpuscles in a volume of saline solution equal to that of the serum removed, should theoretically reduce the serum protein to 30 per cent. of that originally present, provided there were no renewal of the plasma protein. But there is a fairly rapid flow of protein into the plasma from supplies existing in other tissues, so that the serum protein after three successive bleedings amounts to about 50 per cent. of the quantity ordinarily present. Notwithstanding the fall in protein in the blood-plasma, the quantity of urea increases and the amino-acid nitrogen remains constant. These relations are shown in the following table which compares the

[1] Abderhalden, E.: Z. physiol. Chem., 1913, **88**, 478.
[2] Abel, J. J.: First Mellon Lecture, University of Pittsburgh, 1915, p. 22.
[3] Van Slyke, D. D., and Meyer, G. M.: J. Biol. Chem., 1913–14, **16**, 231.
[4] Kossel, A.: Biochem. Zentralbl., 1906, **5**, 33.
[5] Turner, B. B., Marshall, E. K., Jr., and Lamson, P. D.: J. Pharm. and Exper. Therap., 1915, **7**, 129.

analysis of the normal blood and that obtained after five days of plasmapharesis, during which time one-third of the blood was withdrawn fifteen times, a total amount of bleeding equal to more than fivefold the quantity of blood in the fasting animal.

EFFECT OF PLASMAPHARESIS UPON THE COMPOSITION OF DOG'S BLOOD

	Total Protein	Plasma Protein	Blood-count	Urea N	Amino N
	Per cent.	Per cent.	Millions	Per cent.	Per cent.
Original blood	19.28	6.38	8.50	0.013	0.0047
After five days of plasmapharesis	15.83	2.92	6.50	0.021	0.0059

Plasmapharesis has been practiced in the treatment of chronic nephritis and uremia without benefit to the patients. O'Hare, Brittingham and Drinker[1] used the method 18 times upon 8 patients. They believe the method might possibly have clinical value in cases of acute suppression of the urine where it is a question of tiding over a brief period.

The reaction of the organism which causes an increase in the amount of its protein metabolism after reducing the amount of serum protein is also shown in the experiments of Taylor and Lewis,[2] who withdrew blood repeatedly at hourly intervals and substituted saline for it in a dog. In this manner the quantity of serum proteins was reduced to only 2.7 per cent., although the quantity of amino-acid nitrogen and of urea increased in the serum.

These facts accord with the older work of Bauer[3] in Voit's laboratory, who found an increased nitrogen elimination in the urine following bloodletting.

Kerr, Hurwitz and Whipple[4] find that it requires ten days for the serum proteins to regain their former percentages in a fasting dog after plasmapharesis; if the dog be given meat regeneration requires only five to seven days.

Summarizing this discussion, it becomes clear that though the body is built up of proteins which are aggregates of amino-acids, these same amino-acids occur free in only minimal amounts, 4 parts in 100,000 in blood, for example, and 40 to 80 parts in 100,000 in muscle. The largest quanity of the amino-acids may be found in

[1] O'Hare, J. P., Brittingham, H. H., and Drinker, C. K.: Arch. Int. Med., 1919, **23**, 304.

[2] Taylor, A. E., and Lewis, H. B.: J. Biol. Chem., 1915, **22**, 72.

[3] Bauer, J.: Z. f. Biol., 1872, **8**, 567.

[4] Kerr, W. J., Hurwitz, S. H., and Whipple, G. H.: Am. J. Physiol., 1918–19, **47**, 356

the liver, as much as 150 parts in 100,000, after a protein containing meal. After giving meat in large quantity the amino-acid concentration rises in the blood and liver, but not in the muscles, for in the muscles the amino-acids are either reconstructed into body protein, or into a labile "deposit protein" (see p. 357). When starvation takes place it is obvious that the quantity of protein destroyed may depend upon the protein condition of the cells themselves, and that in the presence of much "deposit protein" this may be metabolized in large quantity during the first few days, as is indicated by a high nitrogen elimination in the urine.

The labile deposit protein must first be converted into amino-acids and carried to the liver. It is the liver which chemically changes amino-acids into urea. The muscles are protected from disintegration because they lack this function.

This principle appears not only in the dog, as before stated, but also in man. This is shown in the experiments of Karl Thomas (see p. 357), narrated by Rubner,[1] although in this work carbohydrates were ingested. The daily diet of a man contained 89 grams of protein nitrogen or 4.5 per cent. of the total protein nitrogen content of his organism. During the last day of this diet the man eliminated 77.7 grams of nitrogen in the urine. Then the man was given a diet of starch and sugar, both of which were free from protein, and the nitrogen elimination in the urines of successive days was determined as follows: 28.3; 10.7; 5.15; 5.16; 4.72; 3.93; 3.46; nine-day interval: 3.06; 2.31; 2.16. The gradual elimination of "deposit protein" with the tendency of the total protein metabolism to fall to lower and lower levels is, therefore, a concomitant of protein starvation. It seems that it is this gradual metabolism of "deposit protein," in addition to the constant and necessary metabolism of the protein built into living substance of the cells, which determines the higher level of the protein metabolism during the early days of fasting.

During true fasting it is quite possible that the full extent of protein metabolism is not measured by the nitrogen in the urine, for it may be that muscle proteins are converted into amino-acids which are transported to other organs, to the heart, for example, for the replenishment of an organ which scarcely loses weight during the ordeal of life without food. Such a procedure would be akin to the development of the genital organs of the salmon already described.

[1] Rubner, M.: Arch. f. Physiol., 1911, p. 61.

It will be perceived that although Voit's term "circulating protein" is, generally speaking, a misnomer, yet it served the useful purpose of sharply differentiating the more resistant behavior of living tissue protein from that of ingested protein, and from the material now known as "deposit protein," ingested protein being very readily, and deposit protein quite readily, metabolized.

This point is furthermore well illustrated by the behavior of gelatin. Voit has demonstrated that although gelatin can never be converted into tissue protein nor retained in the body, its ingestion may in part prevent the combustion of the living protein tissue of the body (see page 190).

The amount of protein metabolized by a starving animal in good condition bears a constant relationship to the total metabolism involved. Even in different animals this constancy is observed. E. Voit[1] calls attention to the fact that the nitrogen elimination is not dependent on the weight of the animal, since a pig of 115 kilos produces 0.06 gram per kilo, whereas a guinea-pig weighing but 0.6 kilo eliminates 0.65 gram of nitrogen per kilo, or ten times as much. However, a comparison of the percentage of the total energy derived from protein in fasting animals in good condition (*i. e.*, with considerable fat) varies within much narrower limits—between 7.3 and 16.5 per cent. This is shown in the following table:

NITROGEN METABOLISM OF DIFFERENT ANIMALS IN STARVATION

Animal	Weight in Kg.	N Elimination in Gm.			Percentage of Calories from Protein
		Total	Per Kg.	Per Sq. M. Surface	
Pig	115.0	6.8	0.06	3.2	7.3
Man	63.7	12.6	0.20	6.4	15.6
Dog I	28.6	5.1	0.18	5.2	13.2
Dog II	18.7	3.8	0.20	4.6	10.7
Dog III	7.2	2.2	0.30	5.2	13.5
Rabbit	2.7	1.2	0.46	4.8	16.5
Goose	3.3	0.8	0.23	3.3	7.4
Fowl	2.1	0.7	0.34	4.2	10.0
Guinea-pig	0.6	0.4	0.65	4.2	10.8

It is evident from the above that an average of 90 per cent. of the energy of the fasting metabolism may be supplied by non-protein material. This material is fat (see page 28).

[1] Voit, E.: Z. f. Biol., 1901, **41**, 188.

THE URINE IN FASTING MEN

The nitrogen output in the urine of previously well nourished men during the early days of fasting is remarkably constant as is witnessed by the following table:

	Cetti[1]	Breithaupt[2]	Succi[3]	J. A.[4]	Succi[5]
1	13.55	10.01	13.81	12.17	17.00
2	12.59	9.92	11.03	12.85	11.20
3	13.12	13.29	13.86	13.61	10.55
4	12.39	12.78	12.80	13.69	10.80
5	10.70	10.95	12.84	11.47	11.19
6	10.10	9.88	10.12	.....	11.01

It is thus evident that if the organism has previously been well nourished, the fasting metabolism is remarkably even, about 13 per cent. of the total energy being derived from protein and 87 per cent. from fat.

During prolonged fasting the nitrogen output sinks much below the figures of the earlier days. Thus a woman twenty-four years old averaged 4.15 gm. from the thirteenth to the twenty-fifth day of fasting.[6] A girl nineteen years old whose esophagus had been occluded by drinking sulphuric acid excreted 2.8 grams of nitrogen on the sixteenth day of fasting.[7] An invalid of Tuczec's[8] averaged 4.25 grams of nitrogen between the fifteenth and twenty-first days.

Junkersdorf and Liesenfeld[9] investigated the nitrogen metabolism of two "fasting artists" who fasted 39 days and posed as exhibits in glass cages. Both drank water, took peppermint tablets (which prevented acidosis), and smoked cigarettes. Their results follow:

Hunger Day	Sacco			Mia		
	Weight	Loss of Weight	Urine N	Weight	Loss of Weight	Urine N
	Kg.	Per Cent.	Gm.	Kg.	Per Cent.	Gm.
0	65	..	....	59	..	6.20
10	57	12	....	55	6	7.41
20	54	17	3.24	53	10	3.52
30	52	20	4.94	47	20	3.34
39	50	23	4.81	41	31	3.23*

*Day 38.

[1] Munk, I.: Virchow's Arch. f. path. Anat., 1893, **131**, Suppl., 25.
[2] Munk, I.: *Ibid.*, p. 68.
[3] Luciani, L.: "Das Hungern," Hamburg and Leipzig 1890.
[4] Johansson, J. E., Landergren, E., Sondén, K., and Tigerstedt, R.: Skan. Arch. Physiol., 1897, **7**, 54.
[5] Freund, E. and O.: Wiener klin. Rundschau, 1901, **15**, 91.
[6] Seegen T.: Wiener Acad. Sitzber., 1871, **63**, Part 2.
[7] Schultzen, O.: Arch. Anat. u. Physiol., 1863, p. 31.
[8] Tuczec, F.: Arch. f. Psychiat., 1884, **15**, 784.
[9] Junkersdorf, P., and Liesenfeld, F.: Pflüger's Arch. gesam. Physiol., 1926, **214**, 250.

Under Luciani's observation Succi excreted 4.08 grams on the twenty-ninth day, and under E. and O. Freund his nitrogen excretion was 2.82 grams on the twenty-first day. The latter authors say that after this there was a sudden rise in the amount of nitrogen and chlorin in the urine, suggesting the so-called *premortal rise*, which caused them to stop the experiment. About 3 grams of nitrogen in the urine or a daily destruction of 18.75 grams of protein would seem to be the lowest extreme of protein metabolism in the emaciated organism after a prolonged fast. The analyses by E. and O. Freund of Succi's urine during a fast of twenty-one days was the first complete record of the sort. The daily nitrogen excretion is given in grams below:

DAILY URINARY NITROGEN IN GM. OF SUCCI IN STARVATION

Day	N	Day	N	Day	N
1	17.0	8	9.74	15	5.05
2	11.2	9	10.05	16	4.32
3	10.55	10	7.12	17	5.4
4	10.8	11	6.23	18	3.6
5	11.19	12	6.84	19	5.7
6	11.01	13	5.14	20	3.3
7	8.79	14	4.66	21	2.82

The nitrogen and total sulphur ran together in the urine in the proportion of 17.3N:1S. Munk found the ratio $\frac{N}{S}$ to be 14.7 in Breithaupt and 15.1 in Cetti, and Benedict (see p. 98) found 16.27 during the fifth, sixth, and seventh days of starvation. The sulphur is believed to be derived exclusively from the breaking down of protein.

Interesting work has lately been accomplished by Wilson[1] in a study upon the relation between sulphur and nitrogen metabolism. He states that the usual N:S ratio in muscle is 14.3:1. He finds that when a basal diet (tapioca, 300 gm.; sugar, 100 gm.; olive oil, 100 gm.) containing no protein is constantly taken, and also during fasting, there is a larger elimination of sulphur than is accounted for as arising from muscle breakdown. On the sudden renewal of the basal diet following fasting there is an attempt by the body to conserve its sulphur. The following table shows these relations:

[1] Wilson, H. E. C.: Biochem J., 1925, **19**, 322.

	Urine N Gm.	Urine N:S
4th day of basal diet	3.00	1:12.3
1st " " fasting	2.49	1:11.6
2d " " "	4.87	1:11.3
1st " " basal diet	6.94	1:17.3
2d " " " "	4.48	1:16.9
3d " " " "	3.00	1:10.4

It seems that there may be active preferential retention of sulphur by the tissues when the basal protein-free diet is administered after 2 days of fasting. This leads to the surmise that at times the body may tend to retain its sulphur-containing cystin, which is so essential in the oxidation-reduction system of glutathion. It may be that the muscular weakness in starvation is in part due to loss of glutathion from the tissues, just as has been suggested in the case of the cachexia of carcinoma (p. 185).

The nitrogen and total phosphoric acid (P_2O_5) in the urine are not found in the same ratio as that in which they exist in meat (7.6:1), but there is a greater phosphoric acid excretion. This is also true of the calcium excretion. This greater excretion is due to the metabolism of the bones (Munk). E. and O. Freund found that the $\frac{N}{P_2O_5}$ fell from 5.7 on the first day of Succi's starvation to between 4.2 and 4.4 during the subsequent periods. Munk found this value to be 4.4 in Cetti during ten days and 5.1 in Breithaupt during six days (consult table on p. 100).

Albumin is of frequent occurrence in the starvation urine of man and animals.

URINARY ANALYSIS OF VICTOR BEAUTÉ ON THE FIRST, THIRD, TWELFTH, AND FOURTEENTH DAYS OF FASTING
(Weight in grams)

	Day of Fasting			
	1st	3d	12th	14th
Total N	10.51	13.72	8.77	7.78
Urea N	8.96	12.26	6.62	5.99
Ammonia N	0.40	0.73	1.05	0.73
Uric acid N	0.12	0.06	0.17	0.17
Purin base N	0.029	0.032	0.023	
Creatinin N	0.42	0.34	0.30	0.24
Creatin N	0.02	0.09	0.09	0.10
Total S	0.614	0.801	0.577	0.536
Total P_2O_5	2.26	2.98	1.55	1.25
Cl	3.2	1.5	0.18	0.24
Ca	....	0.216	....	0.096
Mg	....	0.131	....	0.037
K	....	1.33	....	0.515
Na	....	0.865	....	0.096

A modern chronicle of the urinary excretion during fasting is presented in an experiment by Cathcart[1] on a professional faster, thirty-one years old, a part of which is reproduced on p. 93.

In this experiment the ammonia excretion rose to meet an accompanying acidosis. The creatinin excretion gradually fell, whereas the creatin excretion (see p. 254) remained quite constant. The ratio between the nitrogen and sulphur elimination averaged 15N:1S, or similar to the relation found in muscle, which is 14N:1S. The relatively large potassium excretion and the small sodium excretion indicated respectively the destruction of body tissues which are all rich in potassium salts and the conservation of the body's sodium chlorid supply.

A communication by Brugsch[2] shows that the quantities of β-oxybutyric acid and aceton in the urine become very great in extreme hunger. The experiment was also made on Succi, between the twenty-third and the thirtieth days of starvation, and showed the following remarkable values:

ACETONURIA IN STARVATION (SUCCI)

Starvation Day	N in Grams	β-oxybutyric Acid in Grams	Aceton in Grams
23d	5.87	9.24	0.569
24th	6.41	8.43	0.410
25th	6.27	9.85	0.463
26th	6.18	5.28	0.569
27th	6.30	11.62	0.525
28th	4.43	6.99	0.339
29th	4.19	9.15	0.242
30th	8.42	13.60	0.115

The excretion of urea nitrogen ran between 54 and 70 per cent., and the ammonia nitrogen between 15.4 and 35.3 per cent. of the total nitrogen in the urine. The high ammonia neutralized the very considerable acidosis.

Grafe[3] reports the excretion of 16.25 and 15.41 grams of urinary aceton bodies during the sixteenth and eighteenth days of fasting in a stuporous patient suffering from catatonic rigidity and lying in deep sleep on these days.

Folin and Denis[4] have described results concerning the development of acidosis in two obese women, patients of Dr. J. H. Means.[5]

[1] Cathcart, E. P.: Biochem. Z., 1907, **6**, 109.
[2] Brugsch, T.: Z. exper. Pathol. u. Therap., 1905, **1**, 419.
[3] Grafe, E.: Z. physiol. Chem., 1910, **65**, 21.
[4] Folin, O., and Denis, W.: J. Biol. Chem., 1915, **21**, 183.
[5] Means, J. H.: J. Med. Res., 1915, **32**, 121.

Mrs. M., weighing 108 kilograms, whose height was 149.7 cm. (4 ft. 1 in.), underwent 3 different periods of fasting, with the following results:

URINE ANALYSIS SHOWING ACIDOSIS IN OBESITY

No. of Fast	Day of Fast	Urine N	β-oxybutyric Acid	NH_3	Acidity in Terms of N/10 Alkali
		Grams	Grams	Grams	Cc.
I	4	9.4	18.47	2.50	695
II	5	5.2	13.54	1.50	655
III	4	4.5	17.34	0.81	300

Headache and nausea were present on these fourth and fifth days of fasting, symptoms which disappeared as if by magic after the patient took one piece of toast and a cup of tea. This is due to the small quantity of ingested carbohydrate (see p. 426). The authors state, "If the preceding subject was fat, our next one, Mrs. B., was a veritable pork barrel." Mrs. B. weighed 178 kilograms and measured 163.5 cm. (5 ft., $4\frac{1}{2}$ in.) in height. She did not show the same intensity of acidosis manifested by the other patient, the largest quantity of β-oxybutyric acid eliminated reaching only 7.2 grams on the seventh day of a third fasting period. From these results it was concluded that obesity itself was not a predisposing cause of acidosis. In general, it was observed that the protein metabolism was low in these persons in whom ample fat was present (see p. 108), that repeating the fast lowered the protein metabolism (see Hawk, p. 111), and also that repeated fastings habituated the organism to the complete oxidation of fats as evidenced by a decrease in the amount of β-oxybutyric acid eliminated on corresponding days of the several fasts. In this connection the observation of Abderhalden and Lampé,[1] that fasting progressively increases the power of dog's blood to split tributyrin, is of significance in showing adaptative power by the organism. Folin and Denis conclude that the method of repeated fasting applied to the obese is safe, harmless, and effective, provided the intensity of the acidosis be carefully followed.

THE ENERGY METABOLISM

If a fasting organism be kept at the same temperature and under the same conditions as regards the performance of external work, the metabolism is remarkably even from day to day.

[1] Abderhalden, E., and Lampé, A. E.: Z. physiol. Chem., 1912, **78**, 398.

Hanriot and Richet[1] showed the even absorption of oxygen and elimination of carbon dioxid during the early days of fasting in man, as is illustrated in this table:

	Liters O_2 per Hour	Liters CO_2 per Hour
After 17 hours' fast	17.4	15.3
" 24 " "	16.85	14.15
" 29 " "	16.05	14.3
" 46 " "	16.9	14.35

Later Lehmann and Zuntz[2] made some experiments on the professional faster Cetti. They analyzed his urine and feces, and also obtained two samples of the carbon dioxid eliminated between 10 and 11 A. M., each period of collection lasting from ten to fourteen minutes. In other words, the carbon dioxid output was determined for only twenty to twenty-six minutes daily. From these data the total day's metabolism was calculated. This apparatus as used by Zuntz has the advantage that it can be made in portable form, and may be carried on the back in mountaineering. The person inspires through a mouth-piece provided with a plate of hard rubber which fits between the lips and the teeth. The nostrils are closed with a clamp. The inspired air is drawn through a valve and the expired air is forced through another valve to a gas-meter. Arrangements are also provided for the gas analysis of portions of the expired air. Trustworthy results are obtained only when the person under investigation is accustomed to the apparatus and the investigator himself is skilled in its use. It is of especial value when pronounced temporary variations in the metabolism are to be measured.

A difficulty with all short time determinations in untrained subjects is the phenomenon of irregular and usually excessive breathing, which leads to the overventilation of the lungs and an excessive output of CO_2. This is what the Germans call *Auspumpung* of CO_2, "pumping out" of CO_2. Some beautiful unpublished work of Cyrus C. Sturgis illustrating this phenomenon is here given by permission. He describes the periods as follows:

Period I. Nine minutes. The individual lay quietly, breathing normally.

Period II. Nine minutes. The respiratory rate was maintained approximately as in Period I, but the subject was instructed to breathe more deeply. The average increase in minute volume was 6 to 8 liters.

Period III. Immediately after the period of overventilation the subject was told to ignore his breathing.

[1] Hanriot, M., and Richet, C.: Compt. rend. acad. sc., 1888, **106**, 496.
[2] Lehmann, C., and Zuntz, N.: Arch. pathol. Anat., 1893, **131**, Suppl., 23.

TABLE SHOWING THE INFLUENCE OF DEEP BREATHING, RESPIRATION RATE UNCHANGED, UPON THE GAS EXCHANGE IN THE LUNGS

(Periods of 9 minutes. Values in gm. per sq. m. of body surface per hr.)

CO_2 Elimination			O_2 Consumption		
Quiet Breathing Period I	Deep Breathing Period II	Quiet Breathing Period III	Quiet Breathing Period I	Deep Breathing Period II	Quiet Breathing Period III
13.02	29.65	6.28	10.94	14.57	9.62
11.26	22.24	8.26	11.20	13.53	10.33
12.45	23.45	7.58	10.55	11.61	9.11
12.92	25.90	7.65	10.91	11.51	10.59
11.36	34.51	4.72	11.44	16.23	8.27
9.63	20.18	5.86	9.12	11.68	7.78
Average...11.77	25.99	6.73	10.69	13.19	9.28
R. Q. = 0.80	R. Q. = 1.43	R. Q. = 0.53			

The average of the resting Period I shows an elimination of 11.77 gm. of CO_2 and the average of all the values in Periods II and III is 16.36 gm. per period, showing *an increase of 39 per cent.* As regards the oxygen, 10.69 gm. were taken in during Period I and an average of 11.28 during Periods II and III, *an excess of only 5.5 per cent.* Deep breathing raises the oxygen pressure in the alveoli; also the elimination of CO_2 increases the affinity for hemoglobin for O_2: futhermore there is the extra oxygen consumption due to the mechanical work of forced respiration. In Period III the oxygen intake is less than in Period I because overventilation in Period II has added to the oxygen supply of the blood, which accumulating CO_2 now causes to be dissociated from hemoglobin, and also because the work of the muscles of respiration is somewhat less.

The respiratory quotients are also misleading, that of 1.43 betokening formation of fat from carbohydrate in huge amount, and that of 0.53 stimulating the imagination of those who believe that fat is convertible into sugar. Neither of these interpretations is true. The results are artificial and due to conditions which must be constantly borne in mind if gross errors are to be avoided (see pp. 157, 672).

The record of the metabolism of Cetti during a ten days' fast was as follows:

METABOLISM OF CETTI IN STARVATION

Fasting Days	Protein Gm.	Fat Gm.	Calories from Protein	Calories from Fat	Calories, Total	Calories per Kilo
1 to 4.....	85.88	136.72	329.8	1288.2	1618	29.00
5 to 6.....	69.58	131.30	267.3	1237.4	1504	28.38
7 to 8.....	66.30	149.35	254.7	1407.3	1662	31.74
9 to 10.....	67.96	132.38	261.1	1247.4	1508	29.26

A very careful experiment on the metabolism of a fasting medical student twenty-six years old was made by Johansson, Landergren,

Sondén, and Tigerstedt.[1] The man fasted five days, doing light work in the respiration apparatus. The metabolism during these days was determined and was similar to that of Cetti.

Reference has already been made to the notable work of Benedict (p. 78), "The Influence of Inanition on Metabolism." Here in seventeen experiments on seven men the metabolism was determined during a fast of two days, and in one instance the starvation period extended over seven days. In these experiments the metabolism of glycogen was for the first time determined. Benedict's fasting individuals were placed in a respiration calorimeter, and in addition to the usual routine the amount of oxygen consumed by them was measured. Knowing the last factor, Benedict was able to calculate the amount of glycogen destroyed by deducting from the total oxygen intake the part necessary to oxidize the protein catabolized, and then, in the light of the knowledge of the respiratory quotient, apportioning the remainder of the oxygen to the non-protein carbon dioxid eliminated in such a way as to indicate the amounts of glycogen and fat destroyed (see p. 68). The heat value of the metabolism thus calculated agreed within $\frac{1}{2}$ of 1 per cent. with the heat as actually measured by the calorimeter in which the man lived, whereas if the non-protein carbon of the first day had been reckoned as fat metabolized, as had heretofore been the custom, the discrepancy would have been as high as 5 per cent. in some instances. This shows the usefulness of a comparison of direct and indirect calorimetry (see p. 62).

The results of Benedict's experiment on an individual who fasted for seven days are here reproduced:

METABOLISM OF S. A. B. DURING A SEVEN-DAY FAST

Day	Grams			Calories				R. Q.	Urine	
	Protein	Fat	Glycogen	Calculated from Metab.	Directly determined	Per Kg.	Per Sq. M.		Ratio N:S	Ratio N:P_2O_5
1.....	73.4	126.4	64.9	1796	1765	29.7	941	.78	19.6	8.55
2.....	74.7	147.5	23.1	1790	1768	29.9	946	.75	18.6	5.55
3.....	78.1	153.0	5.4	1785	1797	30.8	969	.74	17.38	6.34
4.....	69.8	144.7	25.2	1734	1775	30.8	966	.75	16.11	4.83
5.....	65.2	144.7	8.2	1636	1649	29.0	905	.74	16.26	5.23
6.....	64.4	129.8	21.7	1547	1553	27.5	856	.75	16.27	5.19
7.....	60.8	132.5	18.7	1546	1568	28.0	869	.74	16.28	4.87

[1] Johansson, J. E., Landergren, E., Sondén, K., and Tigerstedt, R.: Skan. Arch. Physiol., 1897, **7**, 54.

This experiment reaffirms the principles which have already been enunciated. Benedict found that the pulse-rate showed a distinct tendency to fall. In the above individual the average pulse-rate was 57 on the first fasting day and 51 on the seventh day.

E. Voit[1] gives the following summary of the energy requirements during the early days of starvation in man:

GENERAL TABLE OF STARVATION METABOLISM IN MAN

Day of Fast	Weight Kg.	Energy in Calories			Author
		Total	Per Kg.	Per Sq. M. Surface	
1	70.6	2359	33.4	1112	Pettenkofer and Voit.
1	70.4	2222	31.6	1060	Pettenkofer and Voit.
1 to 5	64.9	2071	31.9	1042	Tigerstedt.
1	59.5	1893	31.8	1012	Zuntz and Lehmann.
1 to 2	56.0	1773	31.7	985	Zuntz and Lehmann.

To this may be added the average results of the many experiments by Benedict:

METABOLISM IN THE EARLY DAYS OF STARVATION

	1st Day	2d Day	3d Day	4th Day	5th Day
No. of experiments	18	17	9	5	2
Average calories per kg	30.7	31.8	31.0	29.6	28.5
Average calories per square meter surface (Meeh)	992	1028	991	938	885

This minimal metabolism requirement of the fasting organism appears remarkably constant in different men.

In a way the results here mentioned are all summarized in the extended work of Benedict[2] upon a subject L., who fasted for thirty-one days. Benedict found no evidence of any disturbance of the higher mental functions of the subject. He found a lowered power of endurance during the fast, but, according to tests made a year later, could discover no lasting evil effect of the fast either upon muscular strength or mental activity. It is recorded that no feces were passed during the entire fast.

[1] Voit, E.: Z. f. Biol., 1901, **41**, 114.

[2] Benedict, F. G.: "A Study of Prolonged Fasting," Carnegie Institution of Washington, Pub. 203, 1915.

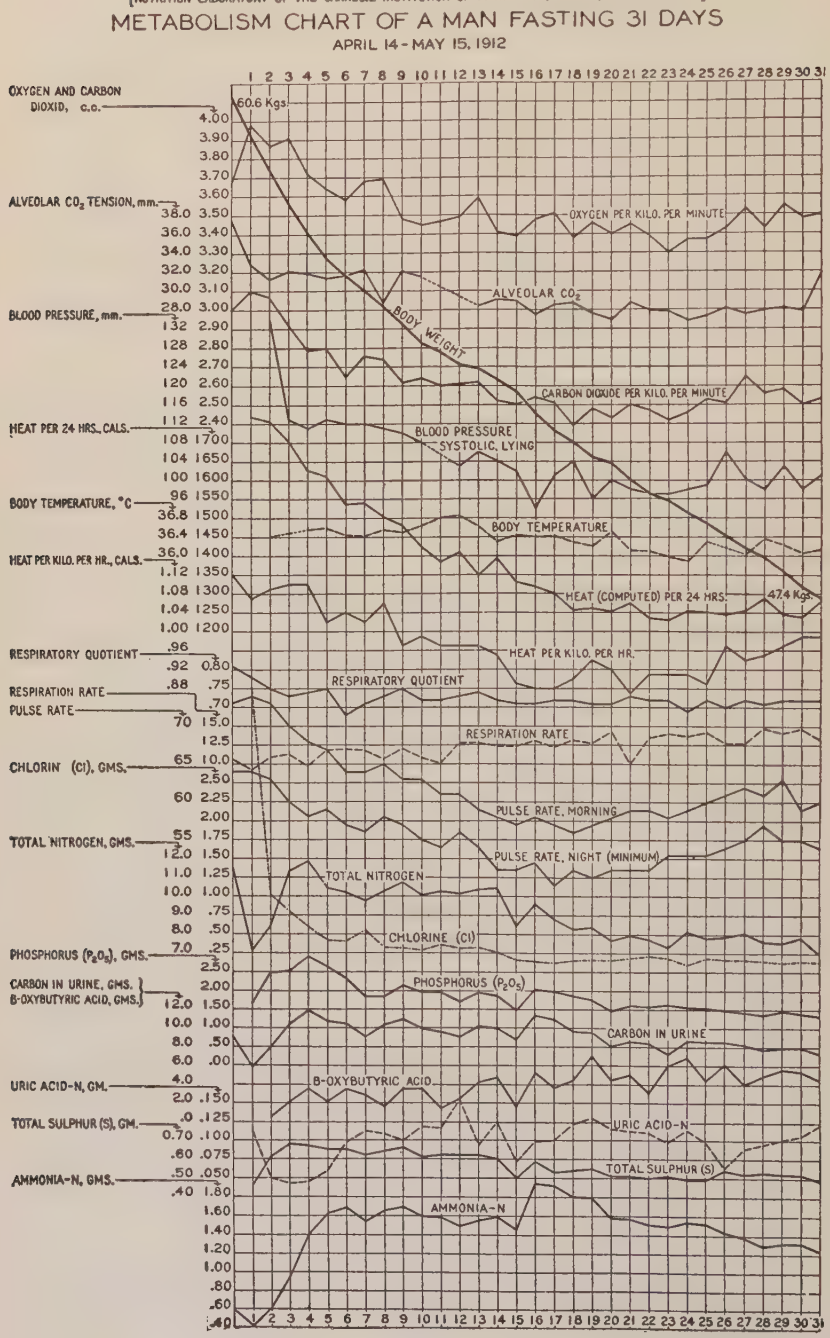

[NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, BOSTON, MASSACHUSETTS]
METABOLISM CHART OF A MAN FASTING 31 DAYS
APRIL 14 - MAY 15, 1912
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
OXYGEN AND CARBON DIOXID, c.c.
ALVEOLAR CO_2 TENSION, mm.
BLOOD PRESSURE, mm.
HEAT PER 24 HRS., CALS.
BODY TEMPERATURE, °C
HEAT PER KILO. PER HR., CALS.
RESPIRATORY QUOTIENT
RESPIRATION RATE
PULSE RATE
CHLORIN (Cl), GMS.
TOTAL NITROGEN, GMS.
PHOSPHORUS (P_2O_5), GMS.
CARBON IN URINE, GMS.
B-OXYBUTYRIC ACID, GMS.
URIC ACID-N, GM.
TOTAL SULPHUR (S), GM.
AMMONIA-N, GMS.
60.6 Kgs.
47.4 Kgs.
OXYGEN PER KILO. PER MINUTE
ALVEOLAR CO_2
BODY WEIGHT
CARBON DIOXIDE PER KILO. PER MINUTE
BLOOD PRESSURE SYSTOLIC, LYING
BODY TEMPERATURE
HEAT (COMPUTED) PER 24 HRS.
HEAT PER KILO. PER HR.
RESPIRATORY QUOTIENT
RESPIRATION RATE
PULSE RATE, MORNING
PULSE RATE, NIGHT (MINIMUM)
TOTAL NITROGEN
CHLORINE (Cl)
PHOSPHORUS (P_2O_5)
CARBON IN URINE
B-OXYBUTYRIC ACID
URIC ACID-N
TOTAL SULPHUR (S)
AMMONIA-N

Fig. 6.

The chart (page 100) illustrates the principal data and a table is given below showing the most important determinations made on the first, eleventh, twenty-first, and thirty-first days of fasting.

The lowest average heat production of the fasting subject when in the bed calorimeter during the night was on the thirtieth day, and amounted to 1025 calories calculated for a twenty-four-hour period, or 661 calories per square meter of surface (Du Bois Height-weight Formula).

During the fast the man lost 277 grams of nitrogen from his body. If one may estimate with Rubner that a man under conditions of

SUBJECT L. HEIGHT, 170.7 CM. ONLY DISTILLED WATER WAS TAKEN DURING THIS FAST

	Day of Fasting			
	1st	11th	21st	31st
Body weight, kg	59.60	53.88	50.49	47.39
Rectal temperature at 7 A. M.	.....	36.54	36.04	35.96
Pulse-rate, morning, awake	74	61	59	60
Hemoglobin in per cent	90	85	88	92
Alveolar CO_2 tension (Haldane)	32.8	.....	28.7	31.8*
Urine: Total solids (all weights in gm.)	43.51	42.05	31.88	27.07
Total N	7.10	10.25	7.93	6.94
Urea N	5.68	7.66	5.54	4.84
Ammonia N	0.41	1.58	1.57	1.24
Uric acid N	0.112	0.116	0.112	0.122
Creatinin + Creatin N	0.48	0.49	0.38	0.32
Chlorin	3.77	0.36	0.18	0.13
P_2O_5	1.66	1.95	1.60	1.32
$N:P_2O_5$	4.28	5.26	4.96	5.26
S	0.46	0.62	0.51	0.49
N:S	15.4	16.5	15.5	14.2
β-oxybutyric acid	.....	1.4	5.0	4.5
Ca	0.217	0.220	0.237	0.138
Mg	0.046	0.072	0.053	0.052
K	1.630	1.006	0.644	0.606
Na	2.070	0.100	0.066	0.053
C:N	0.820	0.936	1.083	1.062
Calories per gm. N	9.15	10.73	11.98	11.53
Loss of flesh calculated from N loss	213	308	238	208
CO_2, night, c.c. per minute	165	128	112	115
O_2, night, c.c. per minute	212	176	154	160
R. Q., night	0.78	0.72	0.73	0.72
H_2O per hour	22.8	18.3	14.6	17.9
Per cent. of calories from protein	10.6	19.6	16.5	14.4
Calories, indirect, twenty-four hours' complete rest	1441	1193	1032	1072†
Calories per square meter (DuBois), twenty-four hours	843	732	653	701‡
Calories per kilogram, twenty-four hours	24.2	22.1	20.4	22.6

* Previous day = 27.8. † Previous day = 1025. ‡ Previous day = 661.

normal nutrition contains 30 grams of nitrogen per kilogram of body weight, then the original nitrogen content of the subject was 1788 grams. A loss of 277 grams would represent 16 per cent. This loss occurred during a period when the heat production fell from 1441 to 1025 calories, a reduction of 29 per cent. It is, therefore, evident that the fall in metabolism reaches greater proportions than does the fall in the mass of protoplasmic tissue.

There seems to be a specific reduction in metabolism coincident with undernutrition (see p. 173). Unfortunately, when food was taken after the fast digestive disturbances marred the records of this subject.

Takahira[1] presents a splendid account of several fasting Japanese. The summary may be given as follows:

Days of Fasting	Days to Recovery	Calories per Sq. M. Body Surface, Du Bois			
		Day Before Fasting	Last Day of Fast	After Recovery	Increase Per Cent.
12	11	37.7	30.5	41.3	+ 9.7
16	..	38.7	30.1		
17	..	37.6	28.3		
26	...	39.2	28.7		
30	30	38.3	26.0	43.4	+11.7

The reduction of metabolism per square meter of surface coincides with the classical pictures of metabolism in fasting and undernutrition. The increased metabolism after recovery was associated with the ingestion of enormous quantities of protein sufficient in itself to have markedly raised the metabolism. The chart showing the metabolism of the individual who fasted 12 days is presented on p. 103.

On the 9th, 10th, and 11th days of re-alimentation the diet contained 33, 31, and 30 gm. of protein nitrogen of which 11, 8, and 5 gm. were added to the body, whereas on the day before the fast the diet contained only 12 gm. of protein nitrogen. The basal metabolism determinations under these conditions are not comparable (see p. 143) with normal standards.

[1] Takahira, H.: "Report from the Metabolic Laboratory, Imperial Government Institute for Nutrition," Tokio, 1925, I, p. 104.

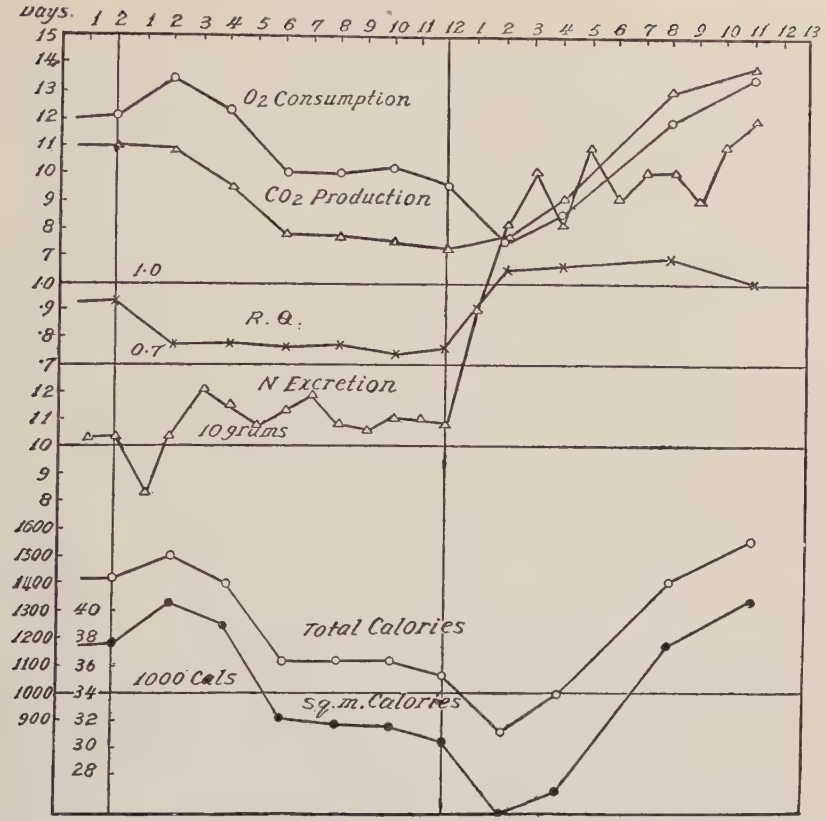

Days. 1 2 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 13
O2 Consumption
CO2 Production
1.0
R. Q.
0.7
N Excretion
10 grms
Total Calories
1000 Cals
Sq. m. Calories

Fig. 7.—Metabolism of a Japanese during fasting and subsequent recovery (Takahira). (Reproduced by permission from E. F. DuBois' "Basal Metabolism in Health and Disease," Lea & Febiger, Philadelphia, 2d ed., 1927, p. 224.)

Additional experiments which show the reduction of metabolism after prolonged fasting are the following:

	Labbe and Stévenin*	Takahira†	Kleitman‡	Benedict
Length of fast in days	43	30	42	31
Original and final body weights, kg.	63–46	58–45.5	65.5–49	60–47
Loss in weight in per cent.	27	21	25	21
Calories per sq. m. start and final.	1039–521	917–626	904–639	1025–661
Loss in cals. per sq. m. in per cent.	49	32	29	36

* Labbe, M., and Stévenin: Compt. rend. soc. biol., 1922, **87**, 607.

† Takahira: "Report from the Metabolic Laboratory, Imperial Government Institute for Nutrition," Tokio, 1925, **1**, 120.

‡ Kleitman, N.: Am. J. Physiol., 1926, **77**, 233.

In Takahira's subject the original basal metabolism of 38.3 calories per sq. m. body surface per hour fell to 26.6 calories, and then

after the fast was broken it rose gradually after 3 weeks of nutrition to the former level of 38.2 calories. Then, following a day on which 30 gm. of N contained in protein were given, on which day 6 gm. of protein N were retained in the body, the basal metabolism reached 43.4 calories per sq. m. an hour.

Kleitman's work upon the faster Hoelzel is of exceptional interest. This man fasted 33 days, then partook of food for a month, and again fasted, this time for 40 days. This is represented in the table.

BASAL METABOLISM IN PROLONGED FASTING IN MAN

(Work on F. Hoelzel. 33-day fast, then 1 month of food, and again 40-day fast)

	Day of Fast and of Post-fast	Wt.	Calories in 24 Hours	
			Total	Per Sq. M.
		Kg.		
Pre-fast average	..	63.1	1517	904
Fast	3	63.0	1545	920
	10	59.1	1282	786
	19	56.1	1177	729
	29	53.4	1095	702
	40	50.0	978	639*
Post-fast	4†	50.4	1110	726
	7	52.0	1306	830
	11	53.9	1285	819
	18‡	58.4	1466	899
	33	64.6	1570	923

* Decrease = 29 per cent.

† Diet: fruits, vegetables, olive oil, butter, cream, and sugar.

‡ Marked edema; on the day before a diet containing 1800 gm. of meat daily was substituted which was continued for 9 days, after which less protein was taken.

It is obvious from the foregoing table that the metabolism of the fasting man did not return to its former level immediately after the ingestion of food. This principle was first shown by Anderson and Lusk[1] in work upon a fasting dog. The facts of the case appear in the following table:

	Weight of Day Kg.	Calories per Hour
Basal metabolism, normal nutrition	9.3	15.5
15th fasting day	7.5	13.0
2d day food containing 14.3 cals. per hr.	7.6	12.6
Day after food containing 28.6 cals. per hr.	7.9	13.0
After 8 days of food containing 28.6 cals. per hr.	8.0	13.9

The food, a mixed diet, was given at one time, and 18 hours afterward the metabolism was measured. It is therefore evident

[1] Anderson, R. J., and Lusk, G.: J. Biol. Chem., 1917, 32, 421.

that *the nutritive condition of the body and not a large influx of food on the day previous determines the height of the metabolism.*

These principles have to do with the understanding of undernutrition, as will appear later.

MINERAL METABOLISM IN FASTING

Benedict calls attention to the fact that there is a parallelism between the amounts of magnesium and of nitrogen eliminated in the urine.

The following analysis of the derivation of the source of the mineral constituents in the urine of Benedict's subject L. may be made. Katz[1] reports upon the quantities of the mineral constituents of human flesh, as obtained from a suicide on the day of death:

MINERAL ANALYSIS OF FRESH HUMAN MUSCLE

PARTS IN 1000

K	Na	Fe	Ca	Mg	P_2O_5	Cl	S
3.20	0.80	0.15	0.075	0.212	4.68	0.70	2.08

On this basis a calculation has been made of the mineral content of the "flesh" computed to have been destroyed on three different days in the fasting subject L., and these calculated values have been compared with the minerals actually excreted in the urines of these days. The following table presents these details:

SUBJECT L. ESTIMATED SALT SUPPLY FROM "FLESH" METABOLIZED ON THE ASSUMPTION THAT THIS WAS MUSCLE TISSUE, COMPARED WITH THE LOSS OF SALTS IN THE URINE. VALUES IN GMS.

	Day of Fast	K	Na	Ca	Mg	P_2O_5	Cl	S
In 308 g. flesh	11	0.986	0.246	0.023	0.065	1.44	0.22	0.64
In urine		1.006	0.100	0.220	0.072	1.95	0.36	0.62
Difference		−0.020	+0.146	−0.197	−0.007	−0.51	−0.14	+0.02
In 238 g. flesh	22	0.762	0.190	0.018	0.050	1.11	0.17	0.50
In urine		0.643	0.066	0.237	0.053	1.60	0.18	0.51
Difference		+0.119	+0.124	−0.219	−0.003	−0.49	−0.01	−0.01
In 208 g. flesh	31	0.665	0.166	0.016	0.044	0.97	0.15	0.43
In urine		0.606	0.053	0.138	0.052	1.32	0.13	0.49
Difference		+0.059	+0.113	−0.122	−0.008	−0.35	+0.02	−0.06

It is apparent that the quantities of potassium, magnesium, and sulphur eliminated in the urine are essentially those which might have been derived from the tissue destroyed. Sodium is constantly retained by the organism, whereas the loss of calcium and P_2O_5 represents osseous destruction. Since bones contain 24.48 per cent.

[1] Katz, J.: Pflüger's Arch. gesam. Physiol., 1896, **63**, 1.

of calcium and only 0.1 per cent. of magnesium, the loss of magnesium from this source would not be appreciable.

It seems clearly evident that the urinary waste of mineral constituents is largely composed of metabolized muscle or tissue analogous in composition to muscle, and of metabolized bone tissue.

CARBOHYDRATE METABOLISM IN FASTING

The blood sugar remains constant during prolonged fasting in dogs, and even rises in the later stages when the metabolism of protein increases.[1]

It has already been set forth that the general metabolism is extremely even in fasting, and it may be added that existing evidence shows that the intermediary metabolism has a similar character. Thus Stiles and Lusk[2] found in a fasting dog made diabetic with phlorhizin that whereas the quantity of nitrogen and sugar eliminated slowly fell, the ratio between the two (the Dextrose : Nitrogen or D: N ratio) remained constant. This is shown in the following table:

CONSTANT RATIO BETWEEN DEXTROSE PRODUCTION AND N ELIMINATION IN STARVATION

Period	D per Hour Gm.	N per Hour Gm.	D: N
15 hours	2.61	0.735	3.56
6 "	....	0.720	
3 "	....	0.683	
12 "	2.39	0.666	3.60
3 "	2.51	0.687	3.65
6 "	....	0.670	
3 "	2.36	0.643	3.66
11 "	2.32	0.642	3.62

The hour-to-hour sugar production from protein is therefore even and constantly proportional to the protein metabolism.

The glycogen of an animal is greatly reduced during starvation, but after seventy-three days it is not entirely removed.[3] Prausnitz[4] reports that a dog weighing 22 kilograms, after fasting for twelve days and after excreting 287 grams of sugar in the urine as the result of phlorhizin injections, still contained 25 grams of glycogen in his body. The writer[5] has found 0.4 gram of glycogen in the liver of a

[1] Morgulis, S., and Edwards, A. C.: Am. J. Physiol., 1924, **68**, 477.
[2] Stiles, P. G., and Lusk, G.: *Ibid.*, 1903, **10**, 77.
[3] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1907, **119**, 119.
[4] Prausnitz, W.: Z. f. Biol., 1892, **29**, 168.
[5] Reilly, F. H., Nolan, F. W., and Lusk, G.: Am. J. Physiol., 1898, **1**, 397.

meat-fed phlorhizinized dog after eleven days of diabetes with an excretion of over 600 grams of sugar. Exercise will greatly reduce the glycogen content, but the only method of completely freeing the organism of glycogen is by tetanus.[1] Zuntz[2] rid a rabbit of glycogen by strychnin convulsions and then kept the rabbit fasting and under the influence of chloral for 119 hours. During this time 5.25 grams of sugar were excreted in the urine, and yet 1.286 grams of glycogen were found in the liver and muscles. This must have gradually arisen from the protein metabolism. The writer[3] made an observation that in a fasting diabetic rabbit tetanus produced an extra elimination of sugar in the urine of 1.1 grams, which undoubtedly was derived from the glycogen content of the organism (see p. 641). The quantity eliminated corresponded to the amount found as glycogen by Zuntz, as above mentioned.

Six rabbits were thus treated. Three died during convulsions. In the other three there was complete paralysis of the muscles of the legs. Only the heart and muscles of respiration remained active. The following day these three rabbits appeared entirely normal, having evidently stored from protein metabolism sufficient glycogen to restore their muscles to motor efficiency according to the theory of Hill and Meyerhof (see pp. 335, 438).

These experiments are so old that modern writers feel privileged to forget them.

LENGTH OF LIFE AND THE CAUSE OF DEATH

The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start. The quantity of fat and protein in an animal at the beginning of starvation or at any time during starvation may be estimated if the day-to-day metabolism be determined and if the whole animal be analyzed for fat and protein at the time of death. The sum of the quantities remaining in the body, and the quantity of waste of previous days, will give the composition of the animal at any definite date during the experiment. E. Voit[4] showed that a rabbit with an original fat content of 7 per cent. lived nineteen days and lost 49 per cent. of his body protein. Another rabbit with an original fat content of

[1] Külz, E.: C. Ludwig's "Festschrift," Marburg, 1891, p. 119.
[2] Zuntz, N.: Verhandl. physiol. Ges. zu Berlin, Arch. f. Physiol., 1893, p. 378.
[3] Lusk, G.: Z. f. Biol., 1898, **36**, 111.
[4] Voit, E.: *Ibid.*, 1901, **41**, 545.

only 2.3 per cent. lived but nine days, while the loss of body protein amounted to 35 per cent. At the death of these rabbits the amount of fat found was very small, and the general vitality toward the end was almost exclusively maintained by the combustion of protein. Other animals, however, which lost 22 to 26 per cent. of their protein contained considerable fat at the time of death (see table, p. 110). E. Voit found that the greater the amount of fat in the body, the less is the protein metabolism. In animals of equal fat content the relation between the amount of fat and the amount of protein oxidized in the cells in starvation is always the same. When there is no fat, protein may burn exclusively. From this it follows that *the quantity of the protein metabolism in starvation depends upon the amount of fat in the body.*

E. Voit[1] has prepared the following table from an experiment of Schöndorff[2] upon a fasting dog. The quotient $\frac{\text{N content}}{\text{Fat content}}$ gives the ratio between these two components of the organism at the time specified. The ratio $\frac{\text{Energy protein}}{\text{Energy total}}$ gives the percentage of the total energy derived from the protein metabolism. The dog died on the thirty-eighth day of his fast:

PROTEIN METABOLISM IN STARVATION AS INFLUENCED BY THE FAT CONTENT OF THE ANIMAL

Starvation Day	Weight in Kg.	N Content / Fat Content	Excreta N in Grams	Energy per Sq. Meter Surface	Energy Protein / Energy Total. Reduced to %
1st to 3d.....	22.4	0.25	7.91	1040	26.5
4th to 13th.....	20.7	0.29	5.38	974	16.2
14th to 15th.....	19.7	0.34	5.70	959	18.1
16th to 23d.....	18.7	0.40	5.71	944	19.1
24th to 30th.....	17.4	0.57	5.92	919	21.3
31st to 35th.....	16.2	0.87	6.62	901	25.6
36th.....	15.7	1.19	7.41	889	29.5
37th.....	15.5	1.34	8.41	887	33.8
38th.....	15.2	1.51	8.89	881	36.6

E. Voit found that the amount of protein metabolism depends so absolutely upon the relation between the amount of fat and protein in the body (the $\frac{\text{N content}}{\text{Fat content}}$) that, knowing this ratio, he says he can estimate the relative protein metabolism. When the ratio rises to 4.84 in the rabbit, then 98.3 per cent. of the total energy may be derived from protein. Had fat still been present in considerable quantity the protein metabolism would have remained low. This is

[1] Voit, E.: Z. f. Biol., 1901, **41**, 520.
[2] Schöndorff, B.: Pflüger's Arch. gesam. Physiol., 1897, **67**, 430.

the law which governs the gradual rise in the protein metabolism during starvation, the "premortal rise" it has been termed. The increased combustion of the protein is due to the requirement for energy in an organism which has a constantly decreasing amount of fat upon which to draw. Thyroidectomized dogs show the "premortal rise" just the same as other dogs.[1] Hári says the rise represents the breaking up of the machinery of the body.

Zuntz[2] described a dog which lived in a constant state of undernutrition for about a year. The energy requirement was as follows:

	Weight, Kg.	Calories per Square Meter
Start	10	931
Eleventh month	4.98	631
Twelfth month	4.1	921

Though the nitrogen in the urine was not collected, Zuntz considered it possible that with the utilization of body fat the metabolism of protein increased, and therefore the heat production increased (see p. 282) toward the end of life.

The actual loss of body weight is greater when protein is the source of energy than when the energy is derived from fat. The metabolism of protein in 100 grams of flesh yields only 80 calories in contrast with 930 calories liberated when 100 grams of fat are oxidized. To obtain equivalent amounts of energy there must, therefore, be a destruction of eleven and a half times more "flesh" by weight than fat.

Rubner[3] has maintained a dog for a long period on a diet of fat which was sufficient in amount to cover the energy requirement. The content of body nitrogen fell from 358.3 grams to 166 grams, a loss of 53.7 per cent. Rubner finds that during the whole period the daily waste of nitrogen is 0.9 gram per 100 grams contained in the body. This "wear and tear" quota is therefore a function of the intensity of the life processes, being proportional to the amount of protoplasmic material present.

What is the cause of death from starvation? It does not seem to be due to an essential change in the composition of the cells themselves, for no chemical alteration has been detected in them.[4] What,

[1] Hári, P.: Pflüger's Arch. gesam. Physiol., 1919, **176**, 123; Mangold, E., Biochem. Z., 1926, **168**, 178.

[2] Zuntz, N.: Biochem. Z., 1913, **55**, 341.

[3] Rubner, M.: Arch. f. Hyg., 1908, **66**, 49.

[4] Abderhalden, E., Bergell, P., and Dörpinghaus, T.: Z. physiol. Chem., 1904, **41**, 153.

then, is the cause of death? The general argument of E. Voit is as follows: It must be due either to a general failure of all the cells or injury of certain organs which are necessary for life. If the first cause were the true one, then death would take place when a certain definite percentage of protein loss occurred. This does not happen, since the body loss at the time of death may vary between 20 and 50 per cent. of its original protein content. When the genital organs of the salmon develop at the expense of the liquefying muscle substance brought them by the blood, not a single muscle cell of the fish is killed, even though these lose 55 per cent. of their protein in the process (Miescher). It seems extremely improbable, then, that a much smaller loss of protein in starvation can be the cause of general cellular death. On the other hand, if death be due to the failure of certain organs especially important to life, the cause is to be found in two factors: Either these organs receive too little nutrition for their proper functioning, or they become so emaciated that they fail in spite of sufficient nutriment. Either the fuel is insufficient or the machine wears out.

The following table gives some answer to this. The general arrangement is in the order of the greater original fat content of the animals:

INFLUENCE OF FAT CONTENT ON PROTEIN METABOLISM AND ON LENGTH OF LIFE IN STARVATION

Animal	First Weight, Kg.	Fat in Per Cent.		Loss in Per Cent.		Days before Death from Starvation	Author
		Start	End	Animal	Body N		
Dog	20.64	19	12	28	22	30	Falk.
Fowl	1.95	26	5	42	26	35	Schmanski.
Guinea-pig	0.67	16	10	38	26	10	Rubner.
Dog	23.05	11	1.7	34	35	38	Schöndorff.
Fowl	1.00	9.1	0.7	39	37	12	Kuckein.
Rabbit	1.51	7.1	0.4	49	49	19	Rubner.
Rabbit	2.53	6.3	0.5	44	49	19	Koll.
Rabbit	2.34	6.3	0.5	41	45	19	Rubner.
Fowl	1.89	2.7	0.7	34	41	9	Kuckein.
Rabbit	2.08	2.3	0.4	35	38	8	Kaufman.
Rabbit	2.99	2.3	0.3	32	35	9	Rubner.

In the first three animals a large amount of fat was present at the time of death, and this had prevented a great tissue waste. Abundant food was therefore available for the cells. The cause of death seems, therefore, to be due to a reduction of activity in one or more organs important for life.

Again, if the protein loss be kept down by administering protein in quantity insufficient for the heating demands of the organism, the animal is kept living largely on his own fat. Schulz[1] in this way kept two dogs alive for twenty-eight and thirty-eight days, with losses of body nitrogen amounting to only 18 and 7 per cent. of the original quantity. The fat present was only 0.4 to 0.5 per cent. at the end. These dogs certainly suffered from no general loss of cell tissue. E. Voit concludes *that death from starvation is primarily due to loss of substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs.*

Schulz[2] and his pupils let a dog which was fat and well nourished fast for twenty-seven days. On the twenty-fifth day the animal manifested weakness, which, on the twenty-seventh day, appeared to threaten its life. Then for a day 400 c.c. of milk were given to the dog and on four subsequent days 300 grams of meat each day. Although these quantities of food were greatly under the quantity required to maintain the dog without loss of body fat, still the animal recovered its strength, added 7.3 grams of protein nitrogen to its body, and then lived during a second period of sixty-one days of starvation. The benefit of the diet was probably due to the disappearance of acidosis and to the high protein metabolism under the influence of ingested carbohydrate, or to carbohydrate arising from protein metabolism itself. During this second fasting period the protein metabolism was on a much lower level than during the first period. Schulz noticed that when the fasting dog still contains considerable fat, protein in the food is readily retained, even though the content of energy ingested be under the body's needs. When, however, the body fat is nearly exhausted, all the ingested protein and some body protein besides is destroyed to provide for the support of the organism. Schulz concluded that death from starvation is due to autotoxemia, a condition which was relieved in the fasting experiment mentioned above by the ingestion of meat.

On the basis of their experiments Howe and Hawk[3] conclude that a "repeated fast" is accompanied by less protein loss from the body than an original fast. Thus, in one dog weighing originally 3.4 kilograms, death was threatened after 15 days of fasting, the loss of body weight having been 45.8 per cent. The animal was then given food

[1] Schulz, F. N.: Pflüger's Arch. gesam. Physiol., 1899, **76**, 379.
[2] Schulz, F. N., and Mangold, E.: *Ibid.*, 1906, **114**, 419–462.
[3] Howe, P. E., and Hawk, P. B.: J. Am. Chem. Soc., 1911, **33**, 253.

for forty-seven days and brought back to the original weight, after which it fasted again and lost 46.8 per cent. in weight during thirty days. During the first fast the daily loss of body nitrogen was 2.3 grams and during the second, 1.31 grams.

THE EFFECT OF FASTING ON VARIOUS ORGANS

The question of what organs are attacked in starvation has attracted attention. Long ago Voit[1] showed that the muscles of a cat which starved thirteen days lost 30 per cent., while heart, brain, and cord lost 3 per cent. only. In normally nourished animals E. Voit finds that the relative weights of the fat-free organs in animals of the same species are very constant. He[2] uses Kumagawa's[3] results to show what percentage the different organs represent in the fat-free organism of a dog before and after a twenty-four-day fast. The third column represents the percentage loss of the fat-free organ in starvation:

LOSS IN WEIGHT OF DIFFERENT ORGANS DURING STARVATION

Organ	Fat-free Animal Contains in Percentage of Weight		Fresh Fat-free Organ Loses in Percentage Weight during a 24 Days' Fast
	Well Nourished	Starvation	
Skeleton	14.78	21.50	5
Skin	10.30	11.29	28
Muscles	53.77	48.39	42
Brain and cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is apparent that the greatest loss is from the glands and the least from the skeleton. The activity of the glands is greatly reduced in starvation. Luciani found that there was no gastric juice formed during Succi's thirty-day fast, but Langley and Edkins[4] find pepsinogen stored within the cells of a cat's gastric glands. The bile flow continues up to the death of the person, but in diminished quantity,

[1] Voit, C.: Z. f. Biol., 1866, **2**, 353.
[2] Voit, E.: *Ibid.*, 1905, **46**, 195.
[3] Kumagawa, M.: "Aus den Mittheil. d. med. Fakultät der kais. Japan. Univ.," Tokio, 1894, **3**, 11.
[4] Langley, J. N., and Edkins, J. S.: J. Physiol., 1886, **7**, 371.

corresponding to the lack of food and the decreasing size of the liver. The writer[1] has noticed a great reduction in the activity of the milk secretion in starving goats, there being a permanent cessation of flow after five days. The percentage of fat increases in the milk, as it does in the blood, liver, and other organs.[2] The fasting organs attract fat from the fat deposits of the body, and it is brought to them by the circulating blood. Glucose is present in the blood up to the last day of life, having its probable origin in a constant production of sugar in protein metabolism. The composition of the plasma of the blood in fasting, as regards its protein constituents, varies slightly from the normal. Lewinski[3] gives the following comparative analyses of blood-plasma of dogs:

100 C.C. BLOOD-PLASMA CONTAIN OF GRAMS N:

		Total	Albumin	Globulin	Fibrinogen
Dog I.	Fasting	0.935	0.621	0.257	0.057
	Fed	0.831	0.511	0.240	0.080
Dog II.	Fasting	0.921	0.313	0.544	0.064
	Fed	1.062	0.515	0.423	0.124
Dog III.	Fasting	1.010	0.467	0.450	0.093
	Fed	0.977	0.475	0.402	0.100
Dog IV.	Fasting	1.096	0.554	0.443	0.099
	Fasting	1.052	0.536	0.324	0.192
	Fed	0.877	0.542	0.248	0.087

The only constant change seems to be a slight increase of globulin during fasting. Burckhardt believes this to be due to the passage of globulins from the tissues to the blood. Robertson[4] reports that in the fasting dog and cat the globulins tend to increase in the blood, whereas in the rabbit, ox, and horse the albumins increase. The percentage of hemoglobin and the number of blood-corpuscles are not appreciably affected. It is evident, then, that the blood in starvation retains the normal composition as regards its nutrient materials, except that it carries fat in increased quantity to the cells. In general the cells are well nourished for the ordinary maintenance of the life functions. Hence the appetite is not an expression of general cellular hunger, but rather the result of a local condition of the gastro-intestinal canal, which stimulates the individual to replenishment.

[1] Lusk, G.: Voit's Festschrift, Z. f. Biol., 1901, **42**, 41.
[2] Rosenfeld, G.: Ergeb. d. Physiol., 1903, **2**, 1, 50.
[3] Lewinski, J.: Pflüger's Arch. gesam. Physiol., 1903, **100**, 631.
[4] Robertson, T. B.: J. Biol. Chem., 1912–13, **13**, 325.

INFLUENCE OF WORK

Frentzel[1] has shown the effect of external work upon the protein metabolism of fasting dogs. One of the dogs did an amount of work corresponding to 216,937 kilogrammeters in three days. The protein metabolism rose during the working hours and continued high on the last day, which was one of complete rest. Frentzel computes that the nitrogen elimination of the last four days (= 20.7 grams) represents an energy equivalent of 220,300 kilogrammeters. This could not cover the work done by the dog if we add to the measured work that which was done by the heart and respiratory muscles. The protein metabolism of four days is therefore entirely insufficient to cover the work done during three. The source of the energy for the work accomplished must be found in an increased metabolism of fat. The increase in protein metabolism above that of rest was not sufficient to supply 7 per cent. of the energy needed to do the work. The record of the dog's nitrogen metabolism is as follows:

INFLUENCE OF WORK ON THE N METABOLISM OF FASTING DOGS

Day	Work or Rest	Food	Grams of N Excreted	
			Per Day	Per Hour
1st to 4th	Rest.	100 g. lard		
5th	Rest.	100 g. "	3.13	0.1304
6th	Rest.	100 g. "	3.52	0.1467
7th	Rest.	Fasting.	3.71	0.1546
8th	Rest.	"	3.99	0.1663
9th	Work.	"	4.97	0.3680* 0.1837†
10th	Work.	"	5.02	0.2750* 0.1960†
11th	Work.		5.63	0.2400* 0.2335†
12th	Rest.	"	5.08	0.2117

* Work. † Rest.

In this experiment, on the 4th day of fasting exercise raised the urinary N from 196 to 240 mg. per hour. In recent experiments of Chambers and Milhorat[2] muscular work raised the urinary N from 128 mg. per hour during rest to 180 mg. during the exercise of running on a treadmill, and the same higher elimination continued during a post-work period of 2 hours. However, this increase in protein metabolism grew less, and on each succeeding day of the fast and

[1] Frentzel, J.: Pflüger's Arch. gesam. Physiol., 1897, **68**, 212.

[2] Chambers, W. H., and Milhorat, A. T.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 170.

on the 8th, 9th, and 10th days of fasting muscular exercise produced no increase whatever in protein metabolism. This corresponds to the results obtained by Frentzel on Day 11 in the table given above. Chambers and Milhorat associate their results with the depletion of the carbohydrate stores of the body. It is not impossible that residual body glycogen is associated with N-containing materials which are liberated when glycogen is dislodged during work in the early days of fasting.

Succi did not show a rise of protein metabolism from the effect of work. The eleventh day of his fast he spent in bed. On the twelfth day he rode a horse for an hour and forty minutes, raced for eight minutes with some students, and gave an exhibition of fencing in the evening. During the day he walked 19,900 steps. The urinary nitrogen on the eleventh day (rest) was 7.88 grams; on the twelfth (work), 7.16; and on the days following 3.50, 5.33, 5.14, 5.05. The work done was evidently at the expense of increased metabolism of fat. That this is the case had already been demonstrated by Pettenkofer and Voit.[1] A fasting man at work showed no increase in his protein metabolism, but the quantity of fat burned rose enormously. This is shown by the following comparison of the number of grams of fat burned:

	Day 8 A. M. to 8 P. M.	Night 8 P. M. to 8 A. M.
Rest during day	116 gm.	94 gm.
Work during nine hours of day period	312 gm.	70 gm.

The fat metabolism during the day of work is two-and-a-half times that of the resting day, and is presumably the source of the energy for the mechanical work accomplished. During the night following the working day the reduction of fat combustion as compared with the night before is due to more profound sleep.

Another phase of the effect of work is shown in the variation between the day and night metabolism of Tigerstedt's fasting medical student, J. A. The average carbon dioxid excretion in grams for two-hour periods during five days of fasting was as follows. The figures showing the elimination during the hours of sleep are printed in black:

	A. M.			P. M.			
Time	10–12	12–2	2–4	4–6	6–8	8–10	10–12
Carbon dioxid (grams)	54.8	57.2	54.1	57.8	59.5	66.4	**46.5**

	A. M.			
Time	12–2	2–4	4–6	6–8
Carbon dioxid (grams)	**37.5**	**39.1**	**40.7**	68.6

[1] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1866, **2**, 459; Voit, C.: *Ibid.*, 1878, **14**, 144.

The nitrogen of the urine was also less during sleep than during the waking hours:

Fasting Day	N in the Urine in Gm.	
	Day	Night (10 p. m. to 10 a. m.)
1st	7.11	4.93
2d	6.87	5.85
3d	6.83	6.65
4th	7.91	5.65
5th	6.36	4.98

Johansson[1] finds that the inequality of night and day metabolism depends on muscular work. Sitting up raises the metabolism, and standing does so still more. Even when one lies in bed, restlessness during the day may increase the metabolism. Zuntz[2] was the first to mention the condition of absolute muscular rest as significant. Even when perfect muscular relaxation ensues there may still be influences, such as light on the retina or sounds, which may act reflexly on the organism and slightly increase the metabolism. Johansson illustrated these variations in the following comparisons between night and day excretion of carbon dioxid of starving men, the night CO_2 being figured at 100:

	Night CO_2	Day CO_2	Author
Complete muscular rest	100	105	Johansson.
Ordinary rest in bed	100	110	Johansson.
Ordinary life (no hard work)	100	142	Tigerstedt.
" " " "	100	128	Pettenkofer and Voit.
" " " "	100	147	Tigerstedt.

Johansson agrees with Tigerstedt that the minimum metabolism of a man in bed is represented by 24 to 25 calories per kilogram daily, and results obtained by Zuntz, Loewy, and others lead to the same conclusion.[3] These were the original observations on the "Grundumsatz" or as it is now called the *basal metabolism.*

The temperature of the fasting organism is usually normal. Luciani found a normal temperature in Succi during this thirty-day fast. The temperature falls only a few days before death. Sondén and Tigerstedt[4] find that the diurnal variations persist during fasting

[1] Johansson, J. E.: Skan. Arch. Physiol., 1898, **8,** 109.
[2] Lehmann, C., and Zuntz, N.: Virchow's Archiv path. Anat., 1893, **131,** Suppl., 26.
[3] Tigerstedt, R.: Skan. Arch. Physiol. 1910, **23,** 302.
[4] Sondén, K., and Tigerstedt, R.: *Ibid.*, 1895, **6,** 136.

in their ordinary rhythm. The average temperature of the medical student J. A. during his five-day fast was but 0.16 degree below his normal temperature when food was allowed him. These diurnal variations are exactly concomitant with the fluctuations of carbon dioxid excretion noted on a previous page. When the carbon dioxid production increases, the temperature rises.

Furthermore, the diurnal variations tend to disappear if the person be kept in a state of muscular rest, so that the output of energy during the day and the night remains the same. In this state the temperature may fall 0.6 degree below the normal on account of the absence of muscle movement.

Inversion of the normal routine of life, so that one sleeps in the daytime and is awake and active at night, brings about an inversion of the curve of body temperature. This is well shown in the monkey.[1]

Benedict,[2] however, was unable to obtain any inversion of the curve of normal body temperature in men who worked during the night and slept during the day.

Gibson[3] traveled half-way round the world in making a trip from New Haven, Connecticut, to Manila, and then returned. He found that the rhythm of daily variation was dependent on the time of the solar day and was independent of the part of the world in which he happened to be.

[1] Galbraith, J. J., and Simpson, S.: J. Physiol., 1904, **30,** p. xx.
[2] Benedict, F. G.: Am. J. Physiol., 1904, **11,** 145.
[3] Gibson, R. B.: Am. J. Med. Sc., 1905, **129,** 1048.

CHAPTER V

THE REGULATION OF TEMPERATURE AND BASAL METABOLISM

It is right and proper, however, that anatomy, physiology and pathology should be given separate places in public libraries, apart from medicine, as these basic disciplines are also correlated with general biology and its branches, with primitive plastic imagery and with the fine arts in general.—F. H. Garrison.

It has been seen that the temperature of a warm-blooded animal is maintained at the normal throughout a fast. Not only this, but it is maintained at the same level, even though the temperature of the outside environment vary from 0° C. and lower to 30° to 35° C. In cold-blooded animals the temperature of the body is only slightly higher than that of their environment at the time. The metabolism of such animals varies with the temperature. The frog in the mud during the winter at a temperature of 4° C. has quite a different metabolism from that which he enjoys during the summer sunshine as he sits on the river-bank or snaps at passing flies. The curve of his carbon dioxid elimination at various temperatures has been made by E. Voit from the analyses of H. Schulz,[1] and is given below:

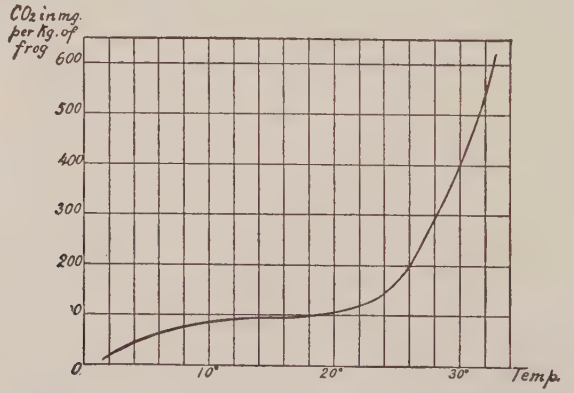


Fig. 8.—CO_2 in milligrams per hour per kg. frog.

Krogh[2] finds that the rise in the metabolism of the normal frog which appears at 20° C. does not show as sharp an ascent in narco-

[1] Schulz, H.: Pflüger's Arch. gesam. Physiol., 1877, 14, 78.
[2] Krogh, A.: Internat. Z. physik.-chem. Biol., 1914, 1, 492.

tized animals, indicating that in the normal frog nervous influences which produce tone begin to make themselves felt at this temperature.

Röhrig and Zuntz[1] first showed that a curarized mammal at ordinary room temperature lost the power of maintaining its body temperature, and the intensity of its metabolism decreased accordingly. Curare prevents the transmission of motor impulses to voluntary muscles.

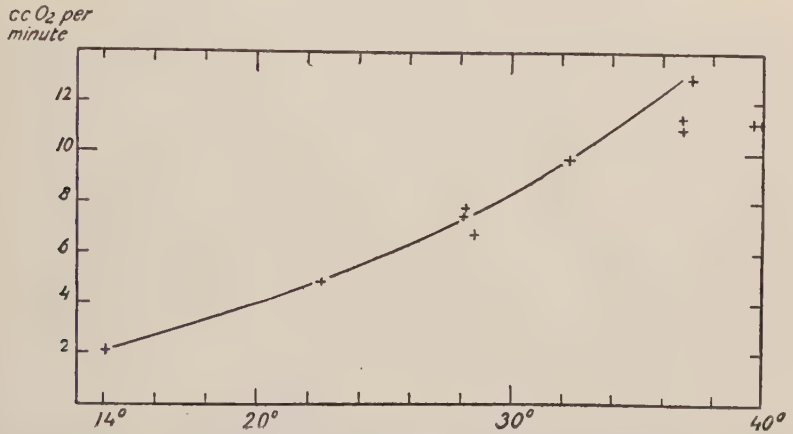


Fig. 9.—Curve of metabolism of a curarized dog subjected to different temperatures (after Krogh).

Krogh states that the curve of oxygen absorption as influenced by body temperature is the same in the anesthetized frog and fish as in the curarized dog. One of Krogh's curves which is given here shows a sixfold increase of oxygen absorption in the curarized dog, indicated by a rise from 2.1 c.c. per minute at a body temperature of 14° C. to 13 c.c. per minute when the body temperature reached 37.2° C.

If the sciatic nerves of a curarized dog be severed, Mansfield and Lukács[2] found that the heat production falls 10 or 15 per cent., but if the sympathetic nerves had previously been severed, cutting the sciatic was without influence upon metabolism. From this they conclude that in the curarized animal sympathetic nerves carry impulses which produce tone in muscles.

Hári[3] states that after cutting the cord in the cervical region in a curarized dog there is a 20 to 30 per cent. decline in the total metab-

[1] Röhrig, A., and Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1871, **4**, 57.
[2] Mansfield, G., and Lukács, A.: *Ibid.*, 1915, **161**, 467.
[3] Hári, P.: Biochem. Z., 1918, **89**, 303.

olism; but that a section of the cord at the sixth thoracic vertebra or one in the lumbar region produces no marked change in metabolism.

The reduction in activity which accompanies reduced body temperature is exemplified by the fact that a cat whose temperature has been artificially reduced to 19° C. may have but one heart beat per minute.[1] At the time of hibernation the marmot lives at the expense of fat. The metabolism may correspond to only one-thirtieth the amount of energy used during the period of activity.[2]

Henriques[3] reports concerning the metabolism of a hedgehog awakening from the winter sleep. The animal weighed 660 grams. Tracheotomy was performed and the respiratory exchange determined during half-hour periods with five-minute intervals between periods, by the Zuntz method. The animal's body temperature was 6.5° C. in the rectum at the start, and the room temperature was 13° C. The animal remained quiet except for characteristic muscle movements resembling shivering which always accompany the awakening of hibernating animals.

The results were as follows:

Period	I	II	III	IV	V
R. Q.	0.62	0.70	0.72	0.71	0.70
Oxygen, c.c., hour and kg.	375	334	851	1983	2083
Rectal temperature at end.	7.5°	9.0°	10.7°	14.1°	26.6° C.

Contrary to other authors, Henriques concludes that the awakening from winter sleep is usually at the expense of fat and not of carbohydrate.

During the entire period 2.21 liters of oxygen were absorbed by the animal. If this had been used for the oxidation of fat the heat produced would have been 10.40 calories (2.21 × 4.7 cals., see p. 68). At the conclusion of the experiment the animal was killed and placed in an ice calorimeter. It was found that the whole animal gave off 13.41 calories. At the beginning of the experiment when the rectal temperature was 6.5° C. the hedgehog contained 3.56 calories (6.5° C. × 660 grams × 0.83 factor for specific heat of body). Therefore 9.85 calories were added to the body during the period of awakening, and these could have been obtained from the 10.4 calories derived from oxidation of fat and still leave a surplus of 0.55 calorie for loss

[1] Simpson, S., and Herring, P. T.: J. Physiol., 1905, **32**, 305.
[2] Regnault, V., and Reiset, J.: An. de chim. et de physic, 1849, **26**, 299.
[3] Henriques, V.: Skan. Arch. Physiol., 1911, **25**, 15.

of heat through radiation and conduction during the period when the body temperature was above the temperature of the environment. It should be remembered, however, that during the earlier periods of low body temperature the organism must have gained heat from its environment.

It may be that the tissues of an awakening marmot hold less CO_2 at 37° than at 6.5° and this factor may be of importance.

Groebbels[1] caused a hedgehog to awake from winter sleep on three successive occasions. After each awakening the animal was returned to a state of complete winter sleep by chilling. The respiratory quotient obtained during the period of awakening decreased with each awakening. They were 0.97, 0.88, and 0.74. It is probable that the respiratory quotient of the awakening period depends on the quantity of available carbohydrate present.

E. Voit[2] has drawn attention to the fact that a curve of increasing metabolism with increasing temperature corresponds to the increasing ability of muscle to contract, and to the increasing effectiveness of enzymotic activity. A high temperature is necessary for the irritability and activity of protoplasm. The warmth of the sunshine increases the irritability of the protoplasm of the tree in the spring, with the resulting development of the foliage. *Warmth, however, is not the cause of the metabolism, but only one of the conditions for it.* In warm-blooded animals the temperature is maintained at a constant level independent of climatic conditions, and this level is a favorable one for the activity of nerve and muscle. It would indeed be inconvenient were the active life of a man dependent upon the temperature of his environment. The essential mechanism for the regulation of the body temperature is nervous. The action of cold on the skin may stimulate its peripheral nerve-endings, which are sensitive to cold, and reflexly effect in the organism a greater heat production and a vasoconstriction of peripheral blood-vessels; the action of heat, on the contrary, effects vasodilatation and production of sweat. It is believed that the cold-blooded progenitors of warm-blooded animals changed their habitat from the sea to the land at a tropical temperature which is at present possessed by their descendants. In the course of development these animals acquired the power to maintain that ancestral temperature which proved favorable

[1] Groebbels, F.: Pflüger's Arch. gesam. Physiol., 1926, **213**, 407.
[2] Voit, E.: Sitzungsber. Ges. f. Morph. u. Physiol., 1896, Heft III.

for the activity of their body substance. The nervous mechanism through which this is accomplished is twofold: First, there is an increased production of heat in the presence of external cold (*the chemical regulation of temperature*); and, second, variations in the quantity of blood supplied to the skin modify loss of heat by radiation and conduction, and variations in the amount of sweat modify the loss of heat by evaporation of water (these are the factors of the *physical regulation of temperature*). The great importance of these two controlling influences will be seen as the subject develops.

THE SURFACE AREA FORMULA OF MEEH

If the body were a mass of cells having the shape of a ball with a constant heat production in its center, it would be easy to calculate its temperature in the different zones of the interior. The loss of heat from the surface would obviously be equal to the heat production if the temperature of the various zones continued constant.

If two balls of the same material, but of unequal size, were equally warm, the smaller would cool more quickly than the larger on account of the relatively greater exposed surface from which heat could be discharged. The heat elimination would be proportional to the surface exposed.

To determine the surface of geometrically similar solids, and hence of animals of similar shapes, the following formula was used by Meeh,[1] in which S = surface and V = volume:

$$\frac{S}{V^{\frac{2}{3}}} = \frac{S\sqrt[3]{V}}{V}$$

Since animals contain the same materials, one may substitute W = weight for V.

Then the value of $\frac{S\sqrt[3]{W}}{W}$ may be empirically determined for each shape or animal, and this value = k. Hence the formula would read:

$$\frac{S}{W^{\frac{2}{3}}} = k \text{ or } S = k\sqrt[3]{W^2}$$

The value of k or the constant in the relationship of weight in kilograms to surface in square meters in each animal has been given by Rubner as follows:

[1] Meeh, K.: Z. f. Biol., 1879, **15**, 425.

Man	0.123
Dog	0.112–0.103
Rabbit	0.129–0.120
Rabbit (without ears)	0.108
Calf	0.105
Sheep	0.121
Cat	0.099
Pig	0.087
Guinea-pig	0.085
Fowl	0.104
Rat	0.091
White mouse	0.114

k in the horse[1] determined upon the live weight is 0.105.

To compute the body surface of a man, for example, the formula $0.123\sqrt[3]{(\text{body-weight in kg.})^2}$ would be employed.

The use of the above formula rendered possible the calculation of the heat elimination per unit of area in fasting animals during periods of twenty-four hours when the temperature of the environment is 15° C. and when moderate voluntary movements are permitted. When the subjects have been previously well fed, and are not emaciated, there is a surprising uniformity of result.

THE LAW OF SURFACE AREA

It is Rubner's law that the metabolism is proportional to the superficial area of an animal.

Erwin Voit[2] has calculated the following general table showing the heat production in resting animals of various sizes at medium temperatures of the environment:

	Weight in Kg.	Calories Produced Per Kilo	Calories Produced Per Sq. M. Surface
Horse	441	11.3	948
Pig	128	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Rabbit	2.3	75.1	776
Goose	3.5	66.7	969
Fowl	2.0	71.0	943
Mouse[3]	0.018	212.0	1188
Rabbit[3] (without ears)	2.3	75.1	917

The *conditions* under which Rubner secured this uniformity were as follows: (1) the measurement of the total energy for 24 hours; (2) the animal was fasting; (3) an environmental temperature of 16°, *i.e.*,

[1] Seuffert, R. W., and Hertel, F.: Z. f. Biol., 1924, **82**, 7.
[2] Voit, E.: *Ibid.*, 1901, **41**, 120.
[3] Rubner, M.: "Energiegesetze," 1902, p. 282.

"room temperature;" (4) the animal was in good nutritional condition; (5) the surface area was measurable.

Rubner states that many observers have not properly regarded the conditions above expressed. It must be remembered that under Rubner's conditions animals and man lead their daily lives in confined spaces, making such ordinary motions as they wish.

The *results* achieved by the knowledge of the law of surface area Rubner[1] classifies as follows: (1) the isodynamic law and the caloric basis of metabolism; (2) discovery of the physical regulation of body temperature; (3) discovery of the specific dynamic action of foods; (4) discovery that metabolism in youth is essentially a surface area phenomenon; (5) discovery that, with the change in bodily condition, *i.e.*, in starvation, changes in metabolism occur which do not follow the surface area law.

In the determination of the *basal metabolism* in modern laboratories the following are the essential conditions: (1) complete muscular relaxation on a comfortable bed beginning 30 minutes before the test; (2) a *post-absorptive* condition, or a time 18 hours after partaking of a readily assimilable mixed diet; (3) an environmental temperature of 25° for an animal or suitable clothing for man; (4) good nutritive condition; (5) measurement of the surface area.

The universality of this law of Rubner's is remarkable. Even at a room temperature of 30° C. where all thermal influence is removed, two guinea-pigs of different sizes will produce heat in proportion to their surface. In this case there is a minimum of heat production determined for the resting organism according to the law of superficial area.

When this discovery was first made, the interpretation was offered that the variation in the metabolism of different animals in proportion to the skin area was due to the "chemical regulation" brought about by the specific sensory influences of cold proceeding from a definite area of surface. Before this Regnault and Reiset had noted that the heat production of sparrows per unit of weight was tenfold that of fowls, a phenomenon which they asserted was due to the fact that the smaller animals present a relatively larger surface to the surrounding air and thereby experience a considerable chilling, with the consequent generation of sufficient heat to maintain the normal body temperature. *This explanation fell when Rubner discovered*

[1] Rubner, M.: Biochem. Z., 1924, **148**, 222.

that at a temperature of 30° C., under which condition all thermal stimulus to the organism ceased, two guinea-pigs of different sizes still produced heat in proportion to their skin areas. A similar fact was noted by Frank and Voit,[1] who found that the administration of curare, which paralyzes the voluntary muscles, scarcely affected the carbon dioxid output of a dog as compared with what was eliminated during ordinary muscular rest, provided the temperature of the animal was maintained at the normal by keeping him in a warmed chamber. The mass of living cells preserved the same metabolism as before, even though a pathway of heat increase had been cut off through paralysis by curare of the motor nerve-endings in the muscles. Keeping the animal in a warmed chamber was necessary in this case, for Roehrig and Zuntz[2] had shown that curarized animals at the ordinary room temperature lost the power of maintaining their body temperature and that their metabolism decreased accordingly. The removal of the chemical regulation caused a behavior toward external temperature similar to that of cold-blooded animals.

In the light of these older experiments the discovery that immersion of a human being in a warm bath (33° to 38°) does not alter his metabolism[3] is quite to be expected.

Although the effect of cold on the skin (inducing chemical regulation) is of itself demonstrably insufficient to account for the "law of skin area," Rubner[4] argues that even at 30° C., when the body is losing heat by means of the dilatation of the blood-vessels and the evaporation of water (physical regulation), the law is still a necessity if the general mechanism for loss of heat in the various animals is the same in all. An infant produces 90 calories per kilogram in twenty-four hours; an adult, 32 calories. Were the metabolism of an adult 90 calories per kilogram, the means of heat elimination through his comparatively smaller surface would have to be materially modified if a normal temperature were to be maintained with comfort.

Though Rubner realized in 1902 that the level of basal metabolism could not be caused by the influence of cooling on the body, yet he believed that the phenomenon of the Law of Surface Area was the result of accommodation to the action of cold to which animals in former ages had been exposed.

[1] Frank, O., and Voit, F.: Z. f. Biol., 1901, **42**, 309. Confirmed by Tangl, F., and Verzár, F.: Biochem. Z., 1918, **92**, 318.

[2] Roehrig, A., and Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1871, **4**, 57.

[3] Benedict, F. G., and Benedict, C. G.: Proc. Nat. Acad. Sc., 1924, **10**, 495.

[4] Rubner, M.: "Energiegesetze," 1902, p. 174.

Further analysis showed Rubner[1] that this evenness of heat production per unit of body surface was not due to any relation between the area of body surface and the area of cell surface within the organism.

Rubner estimates that a man weighing 60 kilograms contains 37.8 kilograms of cell mass, of which 40 per cent. is in muscle tissue, and that while the absorptive surface of the intestinal tract is 1.5 square meters, the surface area of the body cells amounts to 9014 square meters (2.2 acres). There are in 1 kilogram of body weight of man 150.2 square meters of such surface, and each square meter of cell surface produces at least 0.2 calorie per day. In the newborn mouse each square meter of cell surface produces eleven times this amount, or 2.2 calories. It is of interest, also, to note that a kilogram of yeast cells presents a surface area of 600 square meters and at a temperature of 38° C., or that at which mammalian cells exist, 1.25 calories per square meter of surface are produced in twenty-four hours, 8.34 grams of cane-sugar undergoing inversion and fermentation during that interval. This reaction is independent of the strength of the sugar solution within the wide limits of 2.5 to 20 per cent. If the strength of the solution be at the maximum of normal reaction, or 20 per cent., the quantity of sugar utilized in twenty-four hours would be contained in a film $\frac{4}{1000}$ millimeter in thickness surrounding the cells. A like analysis shows that in man, whose cells are bathed in a medium containing 0.1 per cent. of sugar, the quantity necessary for the support of life during one day would be contained in a layer which if spread around the cell would be $\frac{5}{1000}$ millimeter in thickness.

From the calculation of the energy requirement in the food for the life of a man to the energy liberated by a yeast cell in its simple resolution of sugar into alcohol and carbon dioxid is indeed a far cry, except as showing that the energy doctrine, as enunciated by Rubner, unites the world of living things.

Rubner[2] has recently made important contributions to this subject which deserve to be well known. In the first place he shows that when various forms of life are exposed to a temperature of 16° the heat production per kilogram of body substance is extremely variable.

[1] Rubner, M.: Arch. f. Physiol., 1913, p. 240.
[2] Rubner, M.: Biochem. Z., 1924, **148**, 222, 268.

METABOLISM AT USUAL ROOM TEMPERATURE OF 16°

	Weight	Calories per Kg. in 24 Hrs.
A small fish	1.75 gm.	39
Yeast cells	.....	73
Mouse	1.75 gm.	977
Guinea-pig	50 gm.	286
Horse	450 kg.	15

A mouse living in air at a temperature of 16° produces 25 times more heat than a fish of equal weight. Rubner investigated the application of the surface area law in fishes, amphibians, and reptiles and found that it did not hold.

BASAL METABOLISM OF COLD-BLOODED ANIMALS DETERMINED AT 16°

Fishes	Calories per Sq. M. Surface in 24 Hours		Weight	Calories per Sq. M. Surface in 24 Hours
Gm.			Gm.	
0.5	38.8	Frogs and toads	0.8–49	128
2.25	44.3	Lizard (*Lacerta*)	110	45
3.8	26.0	Alligator	1380	47
193	30.4	Lizard (*Uromastix*)	1250	29
245	32.5	Frogs	1.3–600	98
		Turtle	135	64
Average	33.08	Average	...	68.5

The muscular mechanism varies in different cold-blooded animals. A salmon is very active in water just above the freezing point, whereas snakes and frogs are listless at this temperature.

The picture of the relation of the heat production to the surface area changes completely when one considers the relations existing between various mammals, as shown in the table on p. 123.

These comparative figures are valid, Rubner remarks, despite the carping criticism which some individuals feel themselves forced to express. Why is it that the development of a species is so ordered that its requirement of energy is mathematically proportional to the surface area? If surface area is not related to the quantity of energy produced, what is it that brings about these definitely ordered relationships?

Considering the development of offspring, Rubner points out that the aim of growth is to produce a new organism akin to the parent,

not only in form and size, but also similar in energy production, in consequence of which a gradual reduction in the heat produced per kilogram must accompany growth. When the child reaches the same size and shape as the parent, it will also have the same energy production per square meter of surface, even though the surface area has no constant influence upon metabolism. The surface area may be a valid method of measuring metabolism even though it may not be the direct cause of the heat production. Also the cell mass of animals of different sizes manifests an adaptation to different surface areas.

The transformation of a warm-blooded animal from a cold-blooded one is thus pictured by Rubner: (*a*) There would be a development of feathers or hair and, in mammals living in cold water, of subcutaneous fat, all of which are bad conductors of heat. Further, the *physical regulation* of body temperature would be established, by which the distribution of blood at the surface of the skin is regulated in order to control the loss of heat. The surface area here becomes a factor in the behavior of the animal. In hot weather increased evaporation of water from the lungs and skin would cool the body, a property possessed even by frogs and turtles. Through the evaporation of water a frog exposed to an air temperature of 30° maintains a body temperature of 20°. An animal provided with the mechanical arrangements above mentioned may maintain the normal body temperature of a warm-blooded animal if the surrounding environment has a sufficiently high temperature. (*b*) To complete a warm-blooded animal would require the creation of neuroregulatory center in the brain in control of the mechanism of *chemical regulation* by which heat production is increased in the presence of cold. Without this mechanism a warm-blooded animal would be a very incomplete creature whose existence would be strictly limited to life at a high environmental temperature, and when exposed to cold would not be able to maintain its heat production except through muscular movements.

One may recall seeing a cat basking in sunshine in zero weather and contrast its life with that of the alligator, which would freeze under like conditions. Rubner compares the metabolism of a marmot weighing 3.15 kg. during its winter sleep when its body temperature is 10°, with that of the same animal awake with a body temperature of 36.7°.

	Body Temperature	Calories per Kg.	Calories per Sq. M. Surface
Asleep	10 °	2.87	47.5
Awake	36.7°	67.74	1160

At a body temperature of 10° the marmot had a heat production per square meter of surface comparable to that of an amphibian or a reptile, but when its body was warmed to the normal mammalian temperature the heat production rose 25 fold and conformed to the usual surface area standards, as given by Rubner. The figures recall the comparison between the fish and the mouse of equal weight.

This subject has been dwelt upon because the surface area standard as a measure of the basal metabolism has been met with flat denial in certain quarters without, it seems to me, giving due weight to all the facts of the case.

Very interesting are the experiments of Aszódi[1] which compare the sugar consumption per gram and hour of the beating hearts of the rat, guinea-pig, rabbit, cat, and dog. The values for the normal heart were found to be:

Heart of Animal	Glucose used by 1 Gm. Beating Heart per Hr., Mg.	Heart Weight in Per Cent. of Body Wt.
Rat	44	
Guinea-pig	17	0.22
Rabbit	25	0.16
Cat	13	0.29
Dog	5	0.64

Aszódi concludes that in the extirpated beating hearts of dogs and other animals, in each species, the smaller the heart the greater the sugar utilization per gram, as follows from the Law of Surface Area. When different species are compared the matter is complicated by the difference in the relative size of the heart and of the body.

Magnus-Levy[2] made 41 short time respiration experiments on the same man when resting without food. The greatest variations from the mean were −7 and +10 per cent. The calories per square meter per twenty-four hours were 812. In 1912[3] Lusk calculated that the heat production of three quiet and sleeping dogs was 759,

[1] Aszódi, Z.: Biochem. Z., 1927, **185**, 450.
[2] Magnus-Levy, A.: Pflüger's Arch. gesam. Physiol., 1894, **55**, 1.
[3] Lusk G. (with McCrudden, F. H.): J. Biol. Chem., 1913, **13**, 450.

748, and 746 calories per square meter of surface at an environmental temperature of 26° C., that a dwarf produced 775 calories per square meter of surface, and that four out of five sleeping men investigated by Benedict showed an average heat production of 789 calories per unit of area. Only in the sleeping infant seven months old, investigated by Howland, did the metabolism appear out of the ordinary. It reached a level of 1100 calories, and this factor was specifically pointed out as indicating a higher metabolism in the youthful protoplasm than is present in the adult.

In 1924 Lusk and Du Bois[1] computed the surface area on the basis of Meeh's formula $0.112\sqrt[3]{(\text{Wgt. in kg.})^2}$ of 11 female dogs the basal metabolism of which had been carefully and repeatedly determined in the calorimeter. It was found that the average heat production was 772 calories per square meter per day. In 9 dogs the metabolism was within ±10 per cent. of this normal, and in 2 dogs the variations were −14 and +15 per cent. Confirmatory results are given by Kunde and Steinhaus.[2]

If it be permissible to use the Meeh surface area formula in interpreting the results obtained from the metabolism of a young growing hog, one finds a truly remarkable conformity to the law of surface area.[3]

BASAL METABOLISM OF HOG II

(Surface = $9\sqrt[3]{\text{Weight}^2}$)

Experiment No.	Date	Age	Weight	Surface	Urine N per Hr.	R. Q.	Heat Production		
							Per Hr.	Per Day	Per Sq. M. of Surface
	1924	Days	Kg.	Sq. M.	Gm.		Cals.	Cals.	Cals.
1	Dec. 17	70	8.5	0.375	0.044	0.93	16.8	403	1076
2	" 22	75	9.5	0.404	0.044	0.95	18.8	451	1118
3	" 24	77	10.0	0.418	0.044	0.90	19.0	456	1092
	1925								
7	Jan. 12	96	12.3	0.480	0.037	0.87	21.1	506	1056
20	Feb. 2	117	18.1	0.620	0.048	0.79	27.9	670	1080
Average									1085
Difference									3 per cent.

From the 70th to the 117th day of its age the weight of this hog more than doubled, rising from 8.5 kg. to 18.1 kg. The average

[1] Lusk, G., and Du Bois, E. F.: J. Physiol., 1924–25, **59**, 213.
[2] Kunde, M. M., and Steinhaus, A. H.: Am. J. Physiol., 1926, **78**, 127.
[3] Wierzuchowski, M., and Ling, S. M.: J. Biol. Chem., 1925, **64**, 697.

basal heat production was 1085 calories per square meter per day within a variation of ± 3 per cent. The law of surface area is thereby afforded additional support as a fundamental biological principle.

Armsby, Fries, and Braman[1] believe that the law of surface area applies to the basal metabolism of cattle inasmuch as their basal heat production is 964 calories per square meter per day. Benedict and Ritzman[2] deny this. They determine the "standing metabolism" at 1700 calories per square meter per day, then deduct 30 per cent. to give the "lying metabolism," or 1200 calories, and then add 100 calories because their steers were "a little" undernourished. It is evident that the determination of the basal metabolism of steers has not yet been reduced to an exact science.

Cowgill and Drabkin[3] with care and accuracy have employed the Du Bois paper mould method for measuring the surface area of 7 dogs varying in weight from 3.4 to 32.6 kg. and have devised a formula which can be used in measuring exactly the surface area of the animal. The details cannot be given here. Suffice it to say that the formula includes the principle upon which von Pirquet[4] based his *peledisi*, which indicates the nutritive condition of the animal. This factor of the formula the authors call N_{obs}, which is the cube root of the *weight* in grams divided by the *length* in centimeters from the tip of the nose to the point on the tail just above the anus.

$$N_{obs} = \frac{\text{Weight}^{\frac{1}{3}}}{\text{Length}}$$

The maximal value of this found in the dog was 0.34. In emaciated dogs the value was 0.26, but in dogs with good average nutrition 0.29 to 0.31. As a *nutrition corrective factor* the following value was employed:

$$\frac{0.34}{N_{obs}}$$

For the obese this equals 1, for dogs in good nutrition between 1.1 and 1.2, and for thin dogs 1.3 or over.

The final formula arrived at by Cowgill and Drabkin is as follows:

$$\text{Surface (sq. cm.)} = 6.67 \text{ Wgt. in gm.}^{0.70} \times \frac{0.34}{\frac{\sqrt[3]{\text{Wgt. in gm.}}}{\text{Length in cm.}}}$$

[1] Armsby, H. P., Fries, J. A., and Braman, W. W.: J. Agricul. Research, 1918, **13**, 43.
[2] Benedict, F. G., and Ritzman, E. G.: Proc. Nat. Acad. Sc., 1927, **13**, 125.
[3] Cowgill, G. R., and Drabkin, D. L.: Am. J. Physiol., 1927, **81**, 36.
[4] von Pirquet, C. F.: "System der Ernährung," Berlin, 1917.

Using this formula with their dogs of measured surface areas, they obtain the following comparative results:

THE SURFACE AREA OF DOGS, MEASURED AND CALCULATED

No. of Dog	Body Wt.	Length, Nose to Anus	N_{obs}	Surface Area		
				As Measured	Cowgill-Drabkin Formula	Meeh Formula, $S = 0.112\ W^{\frac{2}{3}}$
	Gm.	Cm.		Sq. Cm.	Sq. Cm.	Sq. Cm.
4	3,390	51	0.295	2,320	2,278	2,538
6	5,350	62	0.281	3,284	3,284	3,426
1	5,450	74	0.260	3,815	3,934	3,484
7	10,150	76	0.285	5,070	5,075	5,251
2	17,250	98	0.264	8,104	7,948	7,476
5	25,930	100	0.296	9,106	9,418	9,810
3	32,640	103	0.310	10,763	10,550	11,440
	Average variation in per cent.				±1.77	±6.70
	Maximum variation in per cent.				+3.47	+9.4

Applying this exact formula to two female dogs whose basal metabolisms had been determined many times in the Cornell calorimeter, Cowgill and Drabkin find that the dogs produced 836 calories per square meter of surface (average variation ±5 per cent.), whereas the average basal metabolism of 103 women, as given by Harris and Benedict[1] is 850 calories per square meter of body surface. Here again is witnessed the marvelous uniformity of the Law of Surface Area.

The critical studies of F. G. Benedict[2] led him to conclude "that the metabolism or heat output of the human body, even at rest, does not depend on Newton's law of cooling,[3] and is, therefore, not porportional to the body surface."

It may be said, however, and said very definitely that Rubner, Du Bois, and I are agreed that Newton's law of cooling is not the all controlling influence determining the basal metabolism of mammals at the present day. No modern worker in metabolism has taken that viewpoint.

One may add to this the clear statement of Murlin:[4]

[1] Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington Pub., No. 279, 1919.

[2] Benedict, F. G.: J. Biol. Chem., 1915, **20**, 298.

[3] This law reads, "The quantity of heat gained or lost by a body in a second is proportional to the difference between its temperature and that of the surrounding medium." At the higher temperatures of environment it is obvious this law does not control. See Rubner's experiments on guinea-pigs, p. 125, demonstrating that the effect of cold on the skin is not a sufficient explanation of the law of skin area.

[4] Murlin, J. R.: Science, 1921, **54**, 196.

"The question of causal relationship stands just where it always has stood. If the possession of a large surface in proportion to weight, as in a mouse, is accompanied by a vastly higher heat production per unit of weight as compared with a horse, but the heat production is found to be proportional to the surfaces of two such animals with approximately the same body temperature, it seems to follow that surface loss of heat is at least a more probable *cause* of heat production than body mass. The same is true as between a baby and a man. How else are such facts to be explained?"

Benedict is in agreement with Carl Voit when he concludes that the mass of active protoplasmic tissue determines the height of the metabolism. However, in the search for a standard upon which to calculate what would be the normal heat production of a man suffering from disease it is obviously impossible to measure the mass of active protoplasmic tissue.

Experiments by Moulton[1] show that the nitrogen content of cattle is almost exactly proportional to the surface area of the animal. If the nitrogen content be a measure of protoplasmic tissue, these experiments afford a striking confirmation of the doctrine of Voit that the heat production is proportional to the mass of living cells (see p. 44).

THE SURFACE AREA FORMULA OF DU BOIS

When the Russell Sage Institute of Pathology constructed in Bellevue Hospital an Atwater-Rosa calorimeter copied in the main from the successful models of Benedict, it became absolutely essential that some criterion of normal metabolism be established as a basis from which one could estimate whether the metabolism of a patient under investigation was higher or lower than the normal. The severe criticisms of Benedict upon the method of estimating heat production from the unit of surface led to a very careful review of all the evidence and to new experiments. Du Bois,[2] who took up this work, has used an accurate and ingenious method with which he has been able actually to measure the surface area of normal men. He covered the body surface with tight-fitting underwear, applied melted paraffin, and then paper strips to prevent change in area when the

[1] Moulton, C. R.: J. Biol. Chem., 1916, **24**, 299.

[2] Du Bois D., and Du Bois, E. F.: Arch. Int. Med., 1915, **15**, 868; *Ibid.*, 1916, **17**, 863.

covering was removed. This model of the surface when cut into flat pieces was photographed upon paper in which equal areas were of equal weight. From the weight of paper which received the photographic impression the area of body surface could readily be calculated. A round ball having an area of 0.1490 square meter, when measured by this method, gave an area of 0.1488 square meter. After this fashion E. F. and Delafield Du Bois have discovered that the formula heretofore used for estimating the surface area in man showed an average inaccuracy of 16 per cent. and a maximal variation from the normal of 36 per cent., this being found in very fat individuals. Two new formulæ, a "linear" and a "height-weight" formula, have been evolved which give an average variation of ± 1.5 per cent. and a maximal variation of ± 5 per cent. Using the older formula of Meeh, the heat production per square meter of surface is 833 calories during twenty-four hours, but using the more accurate formula of Du Bois this rises 16 per cent. to 953 calories. In normal adults of various shapes and sizes this is the *basal metabolism* as measured when the individual is resting and before the administration of food in the morning.

The following table presents the results of work upon those persons whose surface areas were actually measured:

COMPARISON OF AREA OF BODY IN SQUARE METERS AS ACTUALLY MEASURED WITH THAT CALCULATED FROM THE DU BOIS FORMULA

Person	Area Measured	Area Calculated	Error in Du Bois Formula	Error with Meeh's Formula	Age	Weight	Height	Basal Calories per Sq. M. Surface per Hour	Remarks
Men:	Sq. M.	Sq. M.	Per Cent.	Per Cent.	Years	Kg.	Cm.		
Benny L.....	0.8473	0.8512	+0.5	+21	36	24.2	110.3	33.0	A cretin.
Morris S.....	1.6720	1.6938	+1.3	+17	21	64.0	164.3	41.2	Normal.
R. H. H.....	1.8375	1.7680	−3.8	+ 7	22	64.1	178.0	40.9	Normal.
E. F. D. B...	1.9000	1.8832	+0.9	+14	32	74.0	179.2	39.8	Normal.
Gerald S.....	1.4901	1.4941	+0.3	+ 4.9	17	45.2	171.8	36.7	Diabetes.
R. H. S.....	1.7981	1.7995	+0.1	+ 8.4	21	63.0	184.2	37.4	Normal.
Fabian S.....	1.1869	1.1455	−3.5	+ 6.2	12	32.7	141.5		
R. L. (Legless)	1.4299	1.4692	+2.7	+37.0	43	63.8			
Women:									
Mrs. McK...	1.8592	1.8956	+2.0	+36	48	93.0	149.7	37.9	Very fat.
Emma W....	1.6451	1.6128	−2.0	+11.6	26	57.6	164.8	33.3	Normal.
Child:									
Anna M.....	0.3699	0.3592	−2.9	+ 9.3	2	6.3	73.2		

As the "Linear Formula" involved taking 19 measurements, a simpler procedure was sought. The formula $A = W^{\frac{1}{2}} \times H^{\frac{1}{2}} \times$

167.2, in which A = area in square meters, W = weight in kilograms, and H = height in centimeters, was found to give an average error of 2.2 per cent. The average error could be reduced to 1.7 per cent. by using the formula,

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

Based on this formula a chart[1] has been devised by which it is possible to estimate the surface area at a glance. It is reproduced in Fig. 10.

Takahira[2] has used the Du Bois method to measure the surface area of Japanese. One typical result was obtained from a male whose height was 169.6 cm., weight 51 kg., and surface area 15,923 sq. cm. The distribution of area was as follows:

	Area in Sq. Cm.	Distribution Per Cent.
Head	1555	10
Trunk	3973	25
Arms	2323	14
Hands	892	6
Legs	6028	38
Feet	1152	7
Total	15923	100

According to Meeh's formula the area would have been 5.85 per cent. larger, but according to Du Bois the calculation showed it would have been 0.84 per cent. smaller than Takahira actually observed. Takahira's results are in close conformity with those of Du Bois, though he suggests a slight modification in the value of K, changing it from 71.84 to 72.46 for measurements on Japanese. If the older value is used the actual measurement of surface areas agrees with the calculated values with an average variation of ± 1.28 per cent. and a maximum of 3.5 per cent. If the newer value be used,

$$\text{Area} = \text{Hgt.}^{0.725} \times \text{Wgt.}^{0.425} \times 72.46,$$

then these variations are within an average of ± 0.95 per cent. with a maximum of ± 2.64. This is a gratifying confirmation of the work of Delafield Du Bois and E. F. Du Bois. Finally, Takahira modifies the Du Bois formula to read:

$$A = H^{0.718} \times W^{0.427} \times 74.49.$$

[1] Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 863.

[2] Takahira, H.: "Report from the Metabolic Laboratory, Imperial Government Institute for Nutrition," Tokio, 1925. **1**, p. 82.

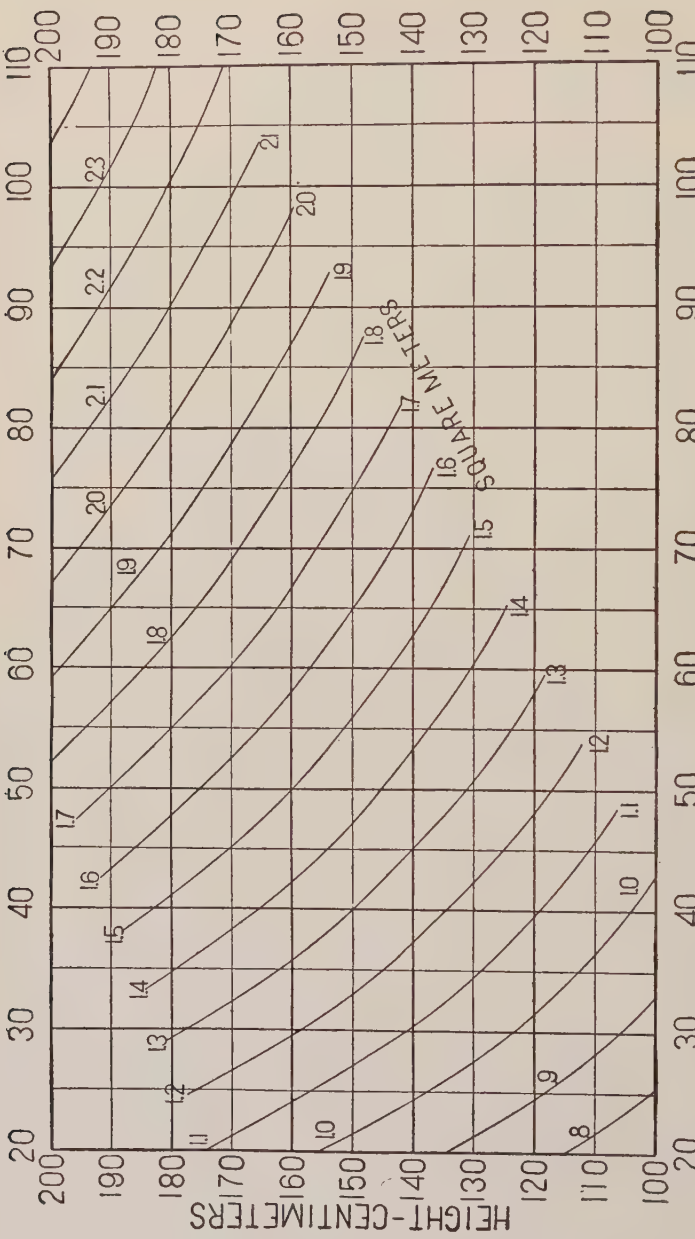


Fig. 10.—Chart for determining surface area of man in square meters from weight in kilograms (Wt.) and height in centimeters (Ht.) according to the formula: Area (Sq. Cm.) = $Wt.^{0.425} \times Ht.^{0.725} \times 71.84$.

This Takahira says gives slightly better results and is merely the expression of belief that the formula of Du Bois is 0.9 per cent. too low.

THE BASAL METABOLISM

The old formula of Meeh gives a close approximation to 34.7 calories per square meter of surface per hour as the measure of the basal metabolism. In people of normal shape this result is so constant that it justifies the conclusion that the basal heat production can be determined by Meeh's formula, whether Meeh's formula for determining surface area is correct or not.

The Du Bois formula gives the following results, the subjects being men between the ages of twenty and fifty years:

	Average Calories per Sq. Meter per Hour	Maximum Variation from Average in Per Cent.
Average 9 normal controls (Du Bois[1])	39.7	+4 and −6
Average 9 normal controls (Means[2])	39.6	+7.6 and −7.1
Average 82 normal controls (Benedict[3])	38.9	usually ±10

As the results of Du Bois were obtained with calorimeter experiments of two or three hours' duration, the figure 39.7 calories per square meter of body surface per hour may be accepted as fairly approximating the normal basal heat production of adult men. The experiments of Means and of Benedict were accomplished with the Benedict unit apparatus and bring confirmatory evidence.

Boothby[4] finds that the metabolisms of 23 patients who recovered their health after operations, and who had been confined in the hospital between twenty and fifty days, most of the time in bed, were within ±10 per cent. of the Du Bois normal standard. This establishes the validity of the use of this measure of the basal metabolism as a criterion of an altered metabolism in hospital patients.

Aub and Du Bois[5] present the following standards of basal metabolism with regard to age and sex. Figure 11 gives a graphic presentation of the data as applied to men.

[1] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 902.
[2] Means, J. H.: J. Med. Res., 1915, **32**, 121; J. Biol. Chem., 1915, **21**, 263.
[3] Benedict, F. G., Emmes, L. E., Roth, P., and Smith, H. M.: J. Biol. Chem., 1914, **18**, 139.
[4] Boothby, W. M.: Oral communication, published by permission.
[5] Aub, J. C., and Du Bois, E. F.: Arch. Int. Med., 1917, **19**, 823, 840.

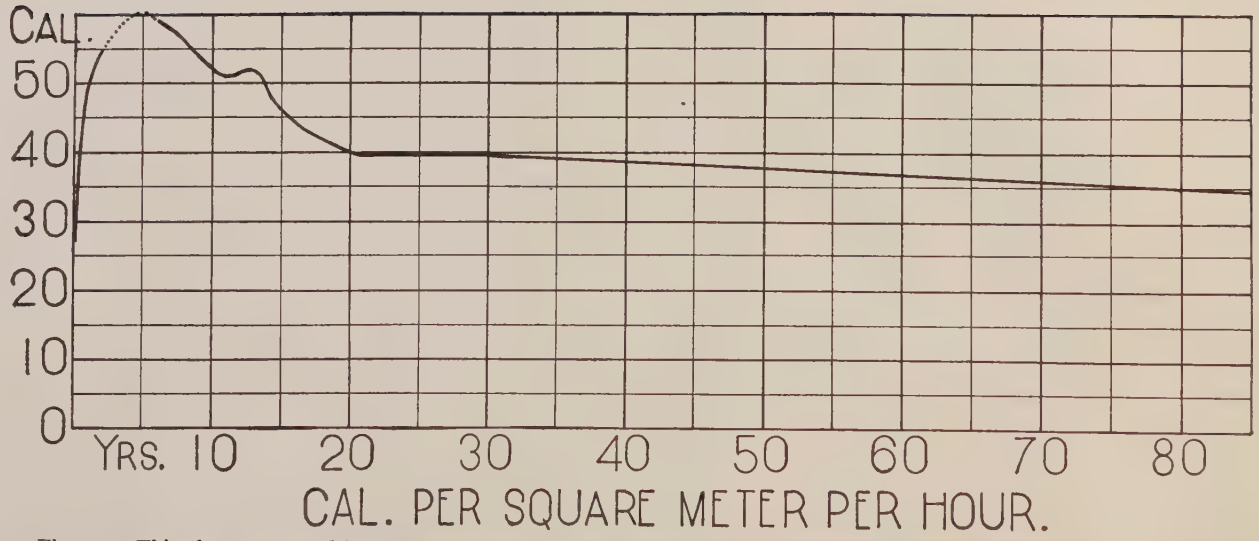


Fig. 11.—This chart, prepared by Du Bois, shows the basal metabolism as measured in calories produced per square meter of body surface per hour from birth until the age of eighty-five years in human males. Between maturity and the eighty-fifth year there is a gradual fall in the intensity of metabolism of 13 per cent. For consideration of the earlier part of the curve, see p. 558.

CALORIES PER SQUARE METER OF BODY SURFACE PER HOUR
(Height-weight formula)

Age, Years	Males	Females
14 to 16	46.0	43.0
16 to 18	43.0	40.0
18 to 20	41.0	38.0
20 to 30	39.5	37.0
30 to 40	39.5	36.5
40 to 50	38.5	36.0
50 to 60	37.5	35.0
60 to 70	36.5	34.0
70 to 80	35.5	33.0

The table shows that boys have a high metabolism (see p. 760), that men have a metabolism which is 7 per cent. higher than women, and that with advancing age there is no longer the same intensity of oxidation as in the prime of life.

Takahira[1] finds that among the Japanese the basal metabolism of males at twenty years of age is 38.1 calories per sq. meter per hour, at thirty it is 37.6, at forty 37.1 and at fifty 36.6. Japanese women are 9 per cent. below these values of calories per square meter of surface.

The greater validity of the Du Bois formula over that of Meeh is shown in the following comparison by Du Bois of the metabolism of fat and thin subjects, computed in larger part from the work of Benedict, Emmes, Roth, and Smith:

	Number of Subjects	Calories per Sq. Meter Average Variation from Normal Standard in Per Cent.		Calories per Kilogram in Twenty-four Hours
		Meeh	Du Bois	
Fat men	5	− 7.6	−4.0	21.9
Thin men	4	+ 6.4	−5.0	29.0
Fat women	7	−12.2	0	19.4
Thin women	6	+ 4.2	−4.0	29.1

It is evident from this analysis that although thin women produce about 50 per cent. more heat per kilogram of body substance than their obese companions, yet per square meter of surface there is little difference.

The metabolism of a fat boy and his thin brother follow the same rule (see p. 317).

[1] Takahira, H.: *Loc. cit.*

In the field so fruitfully developed by Du Bois there appeared in 1919 a second set of standards developed by Harris and Benedict.[1] Their multiple prediction tables are widely used, especially in Europe. The question is whether they really improve the Du Bois standards. If not, it would seem a pity to have two sets of standards. In 1921 Means and Woodwell[2] made the following analysis of the methods used by Du Bois, Dreyer,[3] and Harris and Benedict in predicting metabolism.

COMPARISON OF PREDICTION METHODS BASED ON DATA FROM NORMAL PERSONS

	Average Deviation in Per Cent		
	Du Bois Ht.-Wt. Formula	Dreyer Formula	Harris-Benedict Formula
Series 8 normal men (Means)	−6.2	−2.1	−4.4
" 31 " " (Carpenter *et al*)	−1.7	+0.1	+0.5
" 6 obese (Means)	+3.8	+2.5	−0.1

The authors thus comment on the results:

"We have yet to answer the original question, which method should the clinical calorimetrist use? The answer is obviously that in one sense it is really of small consequence which he uses since the results obtained with the three are so similar. Uniformity, however, is always advantageous and it is best not to abandon an old method for a new one, unless the new presents some material advantage over the old. The Du Bois method is the one in common use today. Since neither the Harris-Benedict nor the Dreyer method has made any material improvement on it we believe it wise to continue with it, and especially in view of the fact that the existence of calorimetry in the clinic of today is due in large measure to the work of Du Bois."

Boothby and Sandiford[4] have strongly supported the Du Bois standards for predicting the basal metabolism. They point out that, as the result of applying mathematics, Harris and Benedict predict that in advanced age men of large size have a higher metabolism than women of the same size, yet women of small size have a higher metabolism than men of small size.

[1] Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington, Pub. No. 279, 1919.

[2] Means, J. H., and Woodwell, M. N.: Arch. Int. Med., 1921, **27**, 608.

[3] Dreyer, G.: Lancet , 1920, **2**, 289.

[4] Boothby, W. M., and Sandiford, I.: "Basal Metabolic Rate Determinations," Philadelphia and London, 1920; J. Biol. Chem., 1922, **54**, 767.

Boothby and Sandiford[1] have given a summary of the basal metabolism data of 8614 persons with special reference to normal standards and also present the following summary of their work on 102 normal persons:

SUMMARY OF 102 NORMAL PERSONS

Decade	Females			Males		
	No. of Cases	Basal Metabolism		No. of Cases	Basal Metabolism	
		Du Bois	Harris and Benedict		Du Bois	Harris and Benedict
		Per Cent.	Per Cent.		Per Cent.	Per Cent.
21–29	19	+0.9	+ 2.3	15	+4.8	+ 6.3
30–39	24	−0.4	+ 3.6	14	−1.4	+ 3.8
40–49	7	−2.1	+ 3.6	5	+3.0	+ 8.6
50–59	9	+1.4	+ 7.4	6	−4.5	+ 4.8
60–69	2	+7.5	+15.5	1	+2.0	+16.0
Average	61	+0.3	+ 4.2	41	+1.0	+ 5.7

MacLeod and Rose[2] find that all of the present prediction standards are too high for women. However, their lowest observation of basal metabolism was selected as the true basal value. They found no correlation between pulse rate and basal metabolism. Their findings are presented in the following table:

A COMPARISON OF THE BASAL METABOLISM OF NORMAL WOMEN WITH PRESENT PREDICTION STANDARDS
(MacLeod and Rose)

Age	No. of Persons	Calories			Deviations from Predicted Values		
		Per Day	Per Sq. M. per Hr.	Per Kg. per Hr.	Aub-Du Bois	Harris-Benedict	Dreyer
20–29	42	1307	33.8	23.0	− 8.5	−5.4	−4.8
30–39	31	1307	34.0	23.1	− 6.9	−2.4	−1.0
40–49	13	1244	31.3	20.2	−12.9	−6.8	−4.8

Aub-Du Bois, 80 per cent. within ±15 per cent.; Harris-Benedict, 88 per cent.

Krogh[3] has suggested that the Du Bois values be reduced 4 per cent. and states that the methods employed by Du Bois are more in accord with biological principles than those of Harris and Benedict. Du Bois[4] believes that the Aub and Du Bois standards of 1917 are

[1] Boothby, W. M., and Sandiford, I.: J. Biol. Chem., 1922, **54**, 783.
[2] MacLeod, G., and Rose, M. S.: Am. J. Physiol., 1925, **72**, 236.
[3] Krogh, A.: Boston Med. and Surg. J., 1923, **189**, 313.
[4] Du Bois, E. F.: "Basal Metabolism in Health and Disease," Philadelphia, 2d ed., 1927, p. 206. Also oral statement.

6 per cent too high when the most modern methods of rest and quiet are today observed. If the lowest of three observations be taken as the true basal metabolism, it is usually lower than the standard. To those who find the method unacceptable because it is based on the Law of Surface Area one may commend the analysis of Boothby, who shows that Benedict's prediction tables may be used to determine surface area quite accurately and also the saying of Means: "Nevertheless, in a broader sense Rubner's Law has never been disproved, and while it may be true that the basal metabolism is not strictly proportional to, nor, perhaps, determined by, surface area, the fact remains that it is more nearly proportional to area than to any other one factor so far discovered."

For the study of metabolism processes it is certainly most fortunate that the unit of surface area eliminates the same amount of heat in the normal adult within 10 per cent. of a determined average. The reason is not clear. But the reasons why the body temperature is constant or why the menstrual period is exactly timed are also not clear, though as facts they are established.

The organism, therefore, preserves the tropical temperature of its cells at the expense of a metabolism which is proportional to the skin area of the individual.

TECHNICAL DETAILS REGARDING THE MEASUREMENT OF BASAL METABOLISM

The Effect of Body Posture and Minor Muscular Movements as Affecting Heat Production.[1]—The subject lying down may move his hand once per minute to his face without appreciably raising his heat production, but crossing the legs every 20 seconds raises it appreciably. Sitting in a comfortable chair increases the basal metabolism only 3 per cent. above that of the recumbent position.

Irradiation with Sunlight or Carbon Arc Light.[2]—No effect on basal metabolism.

Emotional Reactions.[3]—No definite changes. Thirty-four hours without sleep, no change. Jazz band, no change. "Anger" sometimes increases, sometimes diminishes. The changes observed are attributed to muscle tonus or vascular changes involving alteration in the volume of blood flow. *Mental work*[4] is without influence.

[1] Benedict, F. G., and Benedict, C. G.: Proc. Nat. Acad. Sc., 1924, **10**, 498.
[2] Eichelberger, M.: J. Biol. Chem., 1926, **69**, 17.
[3] Landis, C.: Am. J. Physiol., 1925, **74**, 188.
[4] Knipping, H. W.: Z. f. Biol., 1922–23, **77**, 165.

Influence of Emotions on Psychoneurotic War Veterans.[1]—Suggestion that the patient think of some unpleasant war experience caused a marked rise in the basal metabolism of 12 out of 14 ex-soldiers, sometimes accompanied by very fine muscular tremors.

Is Prolonged Bed Rest a Prerequisite?[2]—The basal metabolism of normal men and women, if taken in bed in the morning on awakening, is the same as that taken after preparing their toilet, walking 10 minutes in the cold (−11° C.), walking upstairs and downstairs, *provided* a preliminary rest period of 30 minutes be enforced.

The Effect of a Small Breakfast.[3]—A standard breakfast consisting of bread, 30 gm.; butter, 8 gm.; caffein-free coffee, 200 c.c., containing cane sugar, 10 gm., and milk, 60 c.c.—in all, protein, 4.7 gm.; fat, 9 gm.; carbohydrate, 28.9 gm.; and calories, 222—had the following average effect on the basal metabolism of 3 men: 1st hour, +7 per cent.; 2d hour, +2; 3d hour, +2; 6th hour, −2; 7th hour, ±0; 8th hour, −2 per cent. After the first hour the effect is negligible, though the quantity of food would supply the energy requirement for 3 hours and more. The extra heat produced after administering 222 calories was only 3 or 4 calories, or not over 2 per cent. of the calories ingested.

Effect of Previous Daily Diet.[4]—This is probably more pronounced than is generally thought. It has been emphasized by Krogh.[5] Kleitman's results show the following:

Previous Daily Diet	Basal Calories	
	In 24 Hr.	Per Sq. M.
Oct. 20 Low protein	1369	810
" 24 Diet includes 36–48 egg whites	1570	923
Nov. 4 Low protein	1355	806
" 7 High cal. (3100)	1534	913
" 14 High cal. +30–42 egg whites	1739	1035
" 24 High cal. +30–42 egg whites	1914	1133
Dec. 5 High cal., low protein*	1625	967
" 12 High cal., 1200 gm. meat	1804	1074
" 23 High protein, low cal	1644	979

* Only 20 gm. daily.

It seems fairly conclusively proved that high calories and especially the quantity of protein taken has a decided positive influence on basal metabolism.

[1] Ziegler, L. H., and Levine, B. S.: Am. J. Med. Sc., 1925, **169**, 68.
[2] Benedict, F. G., and Crofts, E. E.: Am. J. Physiol., 1925, **74**, 369.
[3] Soderstrom, G. F., Barr, D. P., and Du Bois, E. F.: Arch. Int. Med., 1918, **21**, 613.
[4] Kleitman, N.: Am. J. Physiol., 1926, **77**, 233.
[5] Krogh, A.: Boston Med. and Surg. J., 1923, **189**, 313.

CHAPTER VI

THE PHYSICAL AND CHEMICAL REGULATION OF BODY TEMPERATURE AND THE INFLUENCE OF CLIMATE

The Greeks had no classical education, but they had the two essentials of true education: first, the ability to express themselves correctly in words, and second, to appreciate their own relation to their surroundings, which latter is science.—Oral remark of E. H. STARLING.

The loss of heat by an organism at rest follows these paths:

1. Conduction and radiation.
2. Evaporation of water from lungs and skin.
3. Warming the food ingested.
4. Warming the inspired air (conduction).

THE MECHANISM OF HEAT LOSS

THE great outlets for heat loss are by conduction and radiation (of which in the dog 97.3 per cent. takes place through the skin and 2.7 per cent. through the lungs[1]) and through the evaporation of water. The losses through warming the food, and through heat of the urine and of solution of urinary constituents, through the feces, and the warming of expired carbon dioxid may be ordinarily disregarded.

The pathway for the loss of heat varies with the temperature of the environment. At a low temperature there is little evaporation of water, and at a temperature of 37° C. there can be no heat loss by radiation and conduction (except by a rise in body temperature), and water evaporation removes the whole of it. In the dog at a high temperature there is spreading out of the limbs to promote heat loss by radiation and conduction, and rapid breathing (polypnea) with extension of the hyperemic tongue to promote evaporation of water. In the horse and in man there is especially an outbreak of sweat which is not possible in the dog, as its skin does not secrete sweat.

Eimer[2] states that 2 gm. of water per hour are lost through the skin of medium sized dogs at medium temperatures, and that pilo-

[1] Rubner, M.: "Energiegesetze," 1902, p. 187.
[2] Eimer, K.: Pflüger's Arch. gesam. Physiol., 1926, **212**, 781.

carpin induces visible sweating on the hairy parts of the animal possibly through rudimentary sweat glands.

Von Willebrand[1] discovered a sudden rise in the elimination of CO_2 through the skin of a man when sweat broke out. This is shown below:

Temperature of Air	H_2O per Hr. Gm.	CO_2 per Hr. Gm.
20.4°	14.6	0.29
31.5°	34.0	0.29
33.5°	Sweat	1.17
34.0°	"	1.35

The increased CO_2 elimination is probably due to the greatly increased blood flow to the skin.

Du Bois[2] finds that the average loss of water from the lungs and skin is 680 grams per day in the normal resting man at an environmental temperature of 23° C. and medium humidity. The evaporation of this amount of water represents an absorption of heat equal to 24 per cent. of the total heat loss. This latter figure is in exact agreement with an average of results previously reported by Benedict and Carpenter.[3] According to Loewy[4] the loss of water of perspiration per square meter of body surface is greatest in the arms, next greatest in the legs (the extremities yielding not far from 75 per cent. of the total), and least from the trunk. The greatest actual loss is, however, from the legs.

The ash of the sweat is mainly common salt. In percentage quantity it is least in the sweat of the leg and most in the trunk. Talbert[5] gives the following analyses:

	Ash Per Cent.
Covered chest: "Heat sweat"	0.34
"Work sweat"	0.44
Covered arm	0.38
Covered leg	0.26
Bare leg	0.22

Sweat produced through mechanical work contains more saline material than does sweat due to heat. And there is a lesser amount of salt in the sweat of the naked surface than in that of the clothed surface. This is an argument against the use of clothes in the tropics.

Loewy also found that in men without sweat glands the evaporation of water from the skin may amount in maximo to 15.6 grams per square meter per hour, or 800 grams for the whole body during a

[1] von Willebrand, E. A : Skan. Arch. Physiol., 1902, **13**, 337.
[2] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 902.
[3] Benedict, F. G., and Carpenter, T. M.: Carnegie Institution of Washington, Pub. 126, 1910.
[4] Loewy, A.: Biochem. Z., 1914, **67**, 243.
[5] Talbert, G. A.: Am. J. Physiol., 1922–23, **63**, 350.

day. In a case described by Richardson[1] of congenital absence of sweat glands, a boy of fourteen could not play in the summer time. He became overheated and had to stop. He wet his shirt to bring relief. When quiet he was comfortable.

Vasomotor reflexes may play an important part in the quantity of water evaporated. Placing the right forearm in cold water reduced the water elimination from the right leg from 3.64 to 3.22 grams per square meter of surface per hour. Washing the right arm with alcohol and ether reduced the water elimination of the right leg to 1.78 grams for the same unit of measurement. In both of these experiments the leg showed an increase above the normal evaporation of water after the removal of the stimulus of cold from the arm.

Benedict and Root[2] and Benedict alone on several occasions has emphasized the fact that the constancy of the "insensible perspiration" is so great that from this water loss the basal metabolism may be quite accurately estimated. Thus a loss of 30 gm. of body weight *per hour* signifies a predicted basal metabolism of 1405 calories per day. However, since the metabolism may be near to 1400 calories daily and the water loss by insensible perspiration 22 or 38 gm. per hour, it does not appear likely that a method involving a ± error of 27 per cent. will ever come into general use.

Generally speaking, there is little difference between the temperature of the inner organs of the body. Heidenhain,[3] confirming earlier work of Claude Bernard, found that in 84 out of 94 experiments with dogs the temperature of the right ventricle was higher than that of the left, two-thirds of the cases showing differences between 0.1° to 0.3°. Claude Bernard[4] states that during digestion the blood of the hepatic vein is 0.1° higher than that of the portal vein. Quincke[5] found that the temperature of the empty stomach of a boy was constantly 0.12° higher than the rectal temperature, and that after the ingestion of 500 c.c. of water at a temperature of 20° C. the original temperature was not regained for seventy to seventy-five minutes. Rancken and Tigerstedt[6] find a temperature in the stomach of a boy with a gastric fistula which averages 0.09° higher and is in maximo 0.2° higher than that of the rectum.

[1] Richardson, H. B.: J. Biol. Chem., 1926, **67,** 397.
[2] Benedict, F. G., and Root, H. F.: Arch. Int. Med., 1926, **38,** 1.
[3] Heidenhain, R.: Pflüger's Arch. gesam. Physiol., 1871, **4,** 558.
[4] Bernard, C.: "Leçons de physiologie opératoire," Paris, 1879, p. 481.
[5] Quincke, H.: Arch. exper. Path. u. Pharm., 1889, **25,** 375.
[6] Rancken, D., and Tigerstedt, R.: Skan. Arch. f. Physiol., 1909, **21,** 85.

Regarding the surface temperature, Henriques and Hansen[1] report the following temperatures at different depths in the fat of the hog's back just one side of the median line:

	C.
1 cm. under the skin	33.7°
2 " " "	34.8°
3 " " "	37.0°
4 " " "	39.0°
Rectal temperature	39.9°

The environmental temperature was, unfortunately, not noted. It must be evident that under these conditions blood coming from the internal organs must lose heat to the cooler surface of the organism.

Benedict and Slack[2] studied the simultaneous records of rectum, vagina, axilla, breast, groin, hand, arm, and mouth, and concluded that aside from the skin temperature a rise or fall in rectal temperature is accompanied by a corresponding rise and fall in temperature of all other parts of the body in man.

Coleman and Du Bois[3] find that in fever, under conditions of a changing blood-supply to the skin, well-covered surface thermometers give a more accurate indication of the average change in body temperature than does the rectal thermometer. As the measurement of the amount of heat gained or lost by an organism during an experiment in which direct calorimetry is determined is effected through the observation of the changes of body temperature, this is an important matter. It may be stated as a general principle that when there is a wide variation in rectal temperature direct and indirect calorimetry do not usually agree as closely as when there is little alteration in body temperature, which indicates that the blood is not at all times so distributed throughout the body that the average rise throughout all the parts is equal to the rise in the rectum alone. Yet, on the whole, the rectal temperature is the best guide available.

Some idea of the activity of the blood flow which equalizes the body temperature may be obtained from the observations of Burton-Opitz,[4] from which may be calculated that an amount of blood equal to the entire amount in the body of a dog traverses the liver every three minutes.

[1] Henriques, V., and Hansen, C.: Skan. Arch. Physiol., 1901, **11**, 161.
[2] Benedict, F. G., and Slack, E. P.: Carnegie Institution of Washington, Pub. 155, 1911.
[3] Coleman, W., and Du Bois, E. F.: Arch. Int. Med., 1915, **15**, 887.
[4] Burton-Opitz, R.: Quart. J. Exper. Physiol., 1912, **5**, 189.

THE REGULATION OF BODY TEMPERATURE

It has been seen that Lavoisier noticed that cold increases the metabolism. This has been abundantly confirmed. The simplest illustration of this action is to be found in fasting animals. Rubner has called this increase of metabolism and, therefore, of heat production the *chemical regulation* of the body temperature (see p. 122). It is the same as burning more coal in the furnace on a cold day in order to maintain the temperature of the house. Voit had previously demonstrated this action in the case of a man (see below).

It has been noted that a constant basic quantity of energy is necessary to maintain the life-processes of a warm-blooded animal situated in a tropical environment. In this case the *energy* of metabolism is directly concerned in maintaining the vibratory motions of the molecules of protoplasm (see p. 391) and heat production is a secondary result. If, now, the organism be subjected to the influence of a cold environment, there is an increased production of *heat* which is directly derived from metabolized substances and the mission of which is to maintain the temperature of the body at the tropical point. It will also be shown in another place how this passive increase in heat production through "chemical regulation," which is induced without visible motion on the part of the animal, may become unnecessary if instead the needed heat be obtained from other sources, as from the increased heat production incident to muscular work or to food ingestion.

Rubner placed a fasting guinea-pig in a bell-jar which was ventilated so that the carbon dioxid production could be determined. The temperature of the bell-jar could be changed by immersing it in water. The following were the results:

ACTION OF CHEMICAL REGULATION IN THE GUINEA-PIG

Temperature of Air	Temperature of Animal	Grams of CO_2 in One Hour per Kg. Animal	Percentage Change of CO_2 for Each 1° C. Rise in Temperature of Air
0.0°	37.0	2.905	−2.33
11.1°	37.2	2.151	
20.8°	37.4	1.766	−1.84
25.7°	37.0	1.540	−2.67
30.3°	37.7	1.317	
34.9°	38.2	1.273	−0.71
40.0°	39.5	1.454	+2.82

It is evident from the table that there was a constant decrease in the metabolism as the air was warmed from 0° to 35° C. The metabolism at 0° was two and a half times that at 30°, an increase as pronounced as is incurred as the result of severe muscular work. The animal at 0° was not observed to move around any more than he did at 30°. These results have been confirmed by Murschhauser.[1] Other experiments confirmed Rubner in the view that the *critical temperature*, or the temperature of the minimum metabolism, lay at 33°. At this point temperature had the least influence on total metabolism. When the temperature is raised from 30° there is at first no increase in the metabolism. This is due to the action of the apparatus for the *physical regulation* of body temperature. As the temperature rises the blood-vessels of the skin become dilated and the evaporation of water from the body is promoted. These factors tend to maintain the normal temperature of the organism by physical means. If the temperature of the air be high, so that the physical regulation be not sufficient to cool the body, then a supernormal temperature ensues. Such a febrile temperature raises the metabolism by warming the cells, as is seen in the table of the experiment in which the guinea-pig was exposed to a temperature of 40°.

Almost identical with the experiment given above and subject to the same analytical interpretation is that of Goto,[2] who exposed a rat to different environmental temperatures and measured its heat production with the following results:

Temperature of Air °C.	Calories per Sq. M.	
	1st Day of Fast	2d Day of Fast
5	1942	1848
13	1628	1571
20	1186	1089
25	976	834
28	845	789
30	896	908
33	1062	982

In the rat Goto finds that the lowest level of basal metabolism is usually at 28° C.

[1] Murschhauser, H.: Z. physiol. Chem., 1912, **79**, 301.
[2] Goto, K.: Biochem. Z., 1923, **135**, 107.

The range of the physical regulation — that is, the period during which external temperature change does not alter metabolism — depends, according to Rubner, on the natural protections which an animal possesses which insure him against heat loss. These are two in number — the hairy covering and the thickness of the layer of subcutaneous fat.

Rubner has shown that the hair of the black cat, black lamb, rabbit, shunk, raccoon, mink, musk-deer, and sheep is of itself relatively light in weight, but that the fur contains a very large quantity of air. The whole of the fur covering of these animals consists of between 97.3 and 98.8 per cent. of air. The fur, therefore, really consists of air with between 1.2 and 2.7 per cent. of hair. The slight conductivity of the fur is principally dependent on this layer of stationary air. If an animal be covered with a fur containing this stagnant air, he will be better protected from loss of heat than if he had none, and also less susceptible to the influence of cold upon the surface of his skin. This protective covering therefore extends the range of the physical regulation.

Rubner[1] gives the following experiment showing the influence of temperature on a small fasting dog with long hair:

ACTION OF CHEMICAL REGULATION IN THE DOG

Day	N in Urine	N in Feces	Total N	C of Respiration	C of Urine	Total C	C from Fat	Calories from Protein	Calories from Fat	Total Calories	Temperature
1st	1.80	0.06	1.86	20.0	1.1	21.0	14.9	46.5	183.6	230.1	20.0°
2d	1.56	0.06	1.62	22.4	1.0	23.4	18.0	40.4	224.6	264.6	15.2°
3d	1.52	0.06	1.58	28.2	1.0	29.1	23.9	39.5	294.7	334.2	7.6°
4th	1.56	0.06	1.62	18.9	1.0	19.9	14.5	40.5	179.0	219.5	30.0°
5th	1.42	0.06	1.48	17.3	0.9	18.2	13.7	37.0	169.3	206.3	25.2°

One observation was made in this experiment on the dog which was not possible in the case of the guinea-pig, and that concerned the nitrogen excretion. The nitrogen excretion for twenty-four hours is not increased by exposing the dog to a temperature of 7.6°. The increased metabolism is entirely at the expense of fat. We have seen that this may also be true of work which may be accomplished at the expense of fat without raising the protein metabolism.

[1] Rubner, M : "Energiegesetze," 1902, p. 105.

Reduced to terms of calories produced per kilogram of dog, the following results are obtained:

Temperature	Calories per Kilo
7.6°	86.4
15.0°	63.0
20.0°	55.9
25.0°	54.2
30.0°	56.2
35.0°	68.5

A temperature of 20° was readily borne by this dog without any increase of his metabolism. The period of unchanging metabolism extended over at least ten degrees between 20° and 30°, during which time the physical regulation alone sufficed to maintain evenly the body's temperature. At 35° a decided increase of heat production set in, on account of the warming of the cells through insufficient heat loss. That the range of the physical regulation of the temperature of this small dog was due to his long hair is shown by the change in his metabolism after shaving him. Rubner shows this in the following table:

Temperature	Calories per Kilo	
	Normal Coat of Hair	Shaved
20°	55.9	82.3
25°	54.2	61.2
30°	56.2	52.0

It is clearly seen that this dog lost his power of physical regulation between 20° and 30° as soon as he lost his covering of hair. His metabolism became like that of the guinea-pig, increasing with a reduction of temperature from 30° downward, an illustration of chemical regulation.

Morgulis[1] determined the metabolism of a dog before and after shaving and exposed to a temperature of 10° C. Shaving the dog caused his heat production to rise from 58.7 calories per kilogram to 111.9 calories in 24 hr. The pulse rate was greatly increased. He believes with Cannon (see p. 159) that shivering is the crude adjustment and the reflex adrenal calorigenic function is the fine adjustment in the case of chemical regulation.

E. Voit[2] shows that the metabolism of a pigeon may be doubled after removing its feathers.

[1] Morgulis, S.: Am. J. Physiol., 1924–25, **71**, 49.
[2] Voit, E.: Sitzungsber. Ges. f. Morph. u. Physiol., 1903, **19**, 39.

Babák[1] finds that if rabbits are shaved and varnished with starch paste their metabolism rises 140 per cent., which increase maintains their body temperature at the normal for several weeks, although the room temperature be between 15° and 20°.

To determine the influence of the second factor, that of the protecting layer of fat, Rubner[2] investigated the influence of temperature on the metabolism of a fasting short-haired dog at a time when he was emaciated, and compared it with the fasting metabolism after the same dog had been fattened. The results were as follows:

Dog (Thin)		Same Dog (Fat)	
Temperature	Cal. per Kilo	Temperature	Cal. per Kilo
5.1°	121.3	7.3°	120.5
14.4°	100.9	15.5°	83.0
23.3°	70.7	22.0°	67.0
30.6°	62.0	31.0°	64.5

It appears from the above that the metabolism of the dog was the same at a low temperature in both cases, but that the minimum metabolism was almost reached at a temperature of 22° when the dog had a protective covering of fat, which was not the case when he was thin. The presence of adipose tissue, therefore, acts in the same way as does a warm fur to extend the range of the physical regulation, and to delay the onset of the chemical regulation of body temperature.

The physical regulation may be increased by certain voluntary acts, such as are observed when a dog exposed to cold lies down and curls himself up in such a way as to offer as small an exposed surface as possible. The contrast to this is offered when on a hot day the dog lies on his back and extends his limbs so as to promote the loss of heat.

Rubner[3] also cites an important modification of metabolism through a variation in the humidity of the atmosphere.

At a medium temperature during fasting (as well as on a medium diet) the metabolism of a dog was practically unaffected by an increase of humidity in the air, as appears below:

Temperature 20.2°	Calories in 24 Hours	Humidity in Per Cent.
Dry day	258.4	34
Humid day	256.6	69
More on dry day	1.8	

[1] Babák, E.: Pflüger's Arch. gesam. Physiol., 1905, **108**, 389
[2] Rubner, M.: "Energiegesetze," 1902, p. 137.
[3] Rubner, M.: *Ibid.*, p. 188.

However, on a liberal diet the metabolism increases on a damp day even at a medium temperature, as for example:

Temperature 20.2°	Calories in 24 Hours	Humidity in Per Cent.
Very dry day	249.4	13
Humid day	261.9	66
More on humid day	12.5	

The increase is 5 per cent.

On a very hot day (on a moderate fat diet) the dog's metabolism is increased by the presence of moisture in the atmosphere.

Temperature 35°	
Calories per Kg.	Humidity in Per Cent.
69.28	9.1
73.54	30.0

Under these circumstances the metabolism rose 6.1 per cent. in the more humid air. There was probably an overwarming of the cells on account of the difficulty of heat loss by evaporation of water. A cold, damp environment of 0° to 5° temperature also favors an increased metabolism. Rubner attributes this action of humidity to the increased conductivity of a hair covering containing moisture, and says that this loss may be partially balanced by a decreased evaporation of water from the lungs.

Murschhauser and Hidding[1] have experimented with guinea-pigs placed in various environmental temperatures and furnished either with perfectly dry air or air completely saturated with moisture. At 35° the well-known influence of air saturated with water increased the body temperature and, therefore, the metabolism. At both 20° and 5° the influence of cold was accentuated by excessive dryness of the air, so that the heat production was about 10 per cent. higher than in moist air at the same temperature. This is explained by the fact that in dry air evaporation of water from the lungs increased the loss of heat by the animal which was compensated for by an increased metabolism.

The metabolism and the manner of heat loss may, therefore, be variously affected by the condition of the atmosphere as regards moisture.

On days of ordinary dryness Rubner[2] calculates the following division of the heat loss in a starving dog under the influence of different temperatures:

[1] Murschhauser, H., and Hidding, H.: Biochem. Z., 1912, **42**, 357.
[2] Rubner, M.: "Energiegesetze," 1902, p. 193.

INFLUENCE OF TEMPERATURE ON MANNER OF HEAT LOSS

Temperature	Calories Lost by Conduction and Radiation	Calories Lost by Evaporation of Water	Total Calories of Metabolism	Humidity Per Cent.
7°	78.5	7.9	86.4	24
15°	55.3	7.7	63.0	34
20°	45.3	10.6	55.9	29
25°	41.0	13.2	54.2	19
30°	33.2	23.0	56.2	14

It is clear that at 7° only a little heat is lost by the evaporation of water and the greater part by conduction and radiation. As the surrounding air becomes warmer the power to lose heat by radiation and conduction diminishes, and the loss through the evaporation of water increases.

Rubner has charted this experiment after making allowances[1] for the varying moisture conditions. The chart is reproduced in Fig. 12, and epitomizes the method of heat loss in a starving dog under the influence of varying temperatures.

The discussion of the metabolism has given a foundation for the understanding of the basic requirement of an organism. The minimum requirement for energy is seen to be present when the fasting organism is surrounded by an atmosphere having a temperature of 30° to 35°. This may be called the *basal metabolism*, the minimum of energy compatible with cell life. This basal metabolism is modified by temperature, by food, and by work, and it is an important factor to keep in mind (see p. 137).

The principles laid down here regarding the lower animals apply equally to man. He too may come under the influence of chemical regulation, although he constantly endeavors to maintain the surface of his skin at a tropical temperature through the use of clothes. His heat loss may, like the dog's, be more difficult if he be covered with a thick layer of fat, and his metabolism is also influenced by atmospheric conditions of moisture, wind, and temperature.

One of the earliest demonstrations of the action of chemical regulation was afforded by Voit, who placed a fasting man weighing 70 kilograms in the Pettenkofer-Voit respiration apparatus and determined the carbon dioxid and nitrogen output for six hours. The person accustomed himself to the given temperature by staying under its influence for some time previous to the commencement of

[1] Rubner, M.: Arch. f. Hyg., 1890, 11, 208.

the experiment. In the cold experiments the ventilating air was derived from the winter atmosphere. For the warm periods the air was artificially heated. The subject of the experiment wore clothing

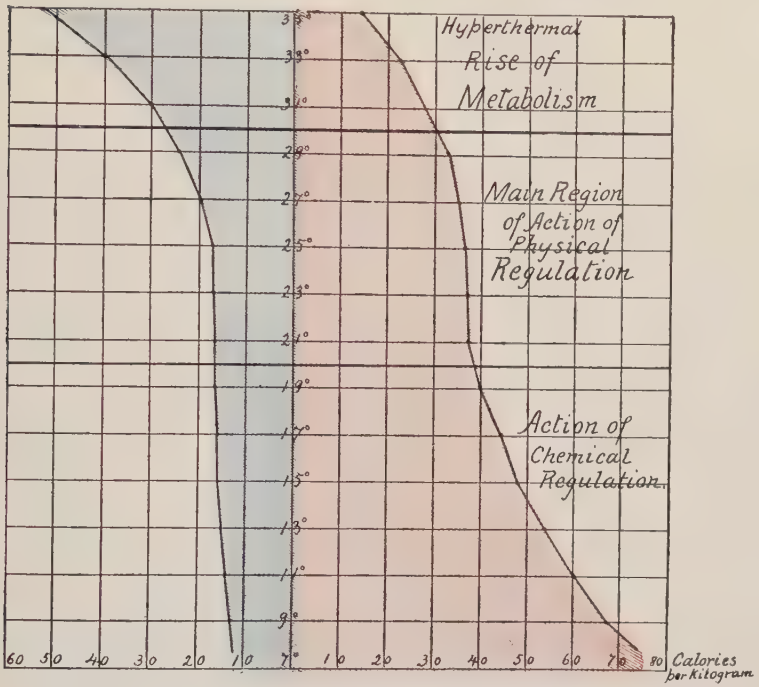


Fig. 12.—Rubner's chart showing the manner of heat loss at different room temperatures in the dog. *Blue*, Heat loss in calories through evaporation of water. *Red*, Heat loss in calories through radiation and conduction.

The distance between opposite points of the curved line represents the total metabolism at a particular temperature.

which was comfortable in the usual warm atmosphere of the laboratory. Voit[1] gives the following results:

EFFECT OF TEMPERATURE ON THE METABOLISM OF A FASTING MAN. SIX-HOUR PERIODS

Temperature	CO_2 Excreted in G.	N in Urine in G.
4.4°	210.7	4.23
6.5°	206.0	4.05
9.0°	192.0	4.20
14.3°	155.1	3.81
16.2°	158.3	4.00
23.7°	164.8	3.40
24.2°	166.5	3.34
26.7°	160.0	3.97
30.0°	170.6	

[1] Voit, C.: Z. f., Biol. 1878, **14**, 80.

The nitrogen elimination remains unaffected by temperature. At the ordinary room temperature there scarcely seems to be any increase in carbon dioxid output, but at the lower temperatures the quantity of the fat metabolism is markedly increased, as shown by the rise of carbon dioxid elimination. The individual sat quietly in a chair, but at a temperature of 4.4° C. could not prevent himself from shivering.

The whole effect of the chemical regulation in man has been attributed by Johansson[1] and also by Sjöström[2] to the additional metabolism due to shivering. Voit did not believe that this could be the cause, nor that the increased respiratory activity could account for the rise in metabolism. Voit believed the increase to be due to a reflex stimulus of cold on the skin which raised the power of the muscle cells to metabolize. Voit's views have been confirmed in Rubner's laboratory[3] in the following series of experiments on a man:

Temperature	CO_2 in Grams per Hour
15°	32.3
20°	30.0
23°	27.9
25°	31.7
29°	32.4

In this experiment there was no shivering at a temperature of 15° and yet the metabolism increased from what it was at 23°.

It has also been shown that cool baths and winds increase the metabolism, which must be effected through the chemical regulation. Lefèvre[4] states that a man who has been inured to it may sit naked for several hours in a cold wind without a reduction of body temperature.

Rubner[5] has measured the effect of baths and douches lasting three and a half to five minutes. When the water has a temperature of 16° he finds that the carbon dioxid elimination may be very largely increased, especially in the case of the douche. The effect of the douche was more marked if taken before breakfast when the intestinal tract was free from food. The results before breakfast were as follows:

[1] Johansson, J. E.: Skan. Arch. Physiol., 1897, **7**, 123.
[2] Sjöström, L.: *Ibid.*, 1913, **30**, 1.
[3] Rubner, M.: "Energiegesetze," 1902, p. 203.
[4] Lefèvre, J.: Compt. rend., soc. biol., 1894, **1**, Series 10, p. 604.
[5] Rubner, M.: Arch. f. Hyg., 1903, **46**, 390.

INFLUENCE OF COLD BATHS ON METABOLISM IN MAN

	Douche 16°. Increase in Per Cent.	Bath 16°. Increase in Per Cent.
Volume of respiration	54.5	22.9
Carbon dioxid excreted	149.5	64.8
Oxygen absorbed	110.1	46.8

A cold bath, especially a douche, will therefore stimulate to a greatly increased metabolism. The mechanical stimulus of the falling cold water apparently acts reflexly to increase the metabolism greatly, as it certainly does the magnitude of the respiration. The respiratory quotient indicates that the increased metabolism is at the expense of the glycogen supply, although the phenomenon of the respiratory *Auspumpung* (see p. 96) of CO_2 from the blood, must here be reckoned with. There is an after-effect which lasts about one and a half hours, indicating an increased metabolism during that time. This may be the expression of the body's attempt to maintain a normal temperature after being somewhat cooled (see also p. 418).

It is obvious that a cold bath will be likely to induce shivering unless by mechanical effort, such as swimming, the metabolism is increased so as to supply calorific energy in another way than through chemical regulation (see p. 421).

A bath of 35° has no effect on metabolism.

Rubner finds that a bath at 44° again increases the metabolism, the increase being, for the volume of respiration, 18.8 per cent., for carbon dioxid 32.1 per cent., and for oxygen 17.3 per cent. This is probably due to the overwarming of the cells. Baths at this temperature find favor among the Japanese.

Lusk[1] found that immersion before breakfast of men in baths at a temperature of 8° which contained cracked ice increased the heat production during a subsequent period of violent shivering to 180 per cent. above the normal. The metabolism was the equivalent of 4500 calories per day for a man weighing 64.7 kilograms. From the respiratory quotient of 0.85 which was found, it may be computed that approximately half of this energy was derived from carbohydrates and half from fat. It is known that cold tends to remove glycogen from the animal body (see p. 641), and it has been shown

[1] Lusk, G.: Am. J. Physiol., 1910–11, **27**, 427.

by Freund and Marchand[1] that a low environmental temperature increases the amount of sugar in the blood.

Schapals[2] brings confirmatory evidence as to the outcome of immersion of men in hot and cold baths:

	O_2 per Minute c.c.	R. Q.	Increase in O_2 in Per Cent.
Normal	223.7	0.78	
Hot bath at 42°	274.0	1.09	15
Normal	278.7	0.78	
Cold bath at 17°	601.0	0.86	116

The higher respiratory quotients obtained may in part be due to a quickened respiration and consequent elimination from the blood of carbon dioxid not belonging to the metabolism of the period. The German term "Auspumpung" properly defines this procedure. In metabolism work this possibility should be always sharply borne in mind (see p. 96).

That a greater metabolism is induced in man after the ingestion of a liter of cold milk than after taking the same amount when it is warm, was shown in Tangl's[3] laboratory, and indicates that an influence may be exerted by *internal cooling*. The body temperature fell 0.25 to 0.8 degree. That such an influence is exerted by cooling was clearly demonstrated by Lusk,[4] who compared the heat production after giving glucose dissolved in cold water and in water at the body temperature to a dog placed in a calorimeter, with the following results:

INFLUENCE OF A COLD DRINK ON METABOLISM

Glucose in Cold Tap-water		Glucose in Water at 38° C.	
Indirect	Direct	Indirect	Direct
Calories 80.33	Calories 75.19*	Calories 75.92	Calories 76.39

* Plus heat for warming the cold water.

When warm water was ingested the computed heat production agreed with that actually found, but when cold water was given there was an increased oxidation, as shown by indirect calorimetry, in order to provide for the body heat lost to the fluid in the stomach (see p. 146).

[1] Freund, H., and Marchand, F.: Arch. exper. Path. u. Pharm., 1913, **73**, 276.
[2] Schapals, F.: Z. exper. Path. u. Therap., 1912, **10**, 222.
[3] Hári, P., and von Pesthy, S.: Biochem. Z., 1912, **44**, 6.
[4] Lusk, G.: J. Biol. Chem., 1915, **20**, 578.

This experiment has been beautifully elucidated by Cannon and his pupils.[1] The denervated heart of a cat is extraordinarily sensitive to epinephrin, 0.0007 mg. per kilogram per minute increasing the pulse rate by 34 beats per minute. Such a denervated cat increases its heart rate when exposed to external cold or after the ingestion of ice water, but *not* if one adrenal is removed and the other denervated. After giving water and ice to 11 human beings so as to produce a "heat debt" of 0.45 calorie per kilogram the heat production rose on an average 16 per cent. and in one case 38 per cent. *without any accompanying shivering*. If shivering occurs there is a quick rise of 60 and 90 per cent.

Cannon thus interprets the phenomenon:

"In the main the body has only one protection against the cold mass of water and ice in the stomach. It must produce heat. This condition is associated with increased adrenal secretion,—a secretion which has calorigenic powers. That with this mechanism in action shivering may not be relied upon, and that in the absence of shivering the metabolism is considerably heightened by cold, we have shown by our experiments. They definitely support the testimony and the arguments of Voit and Rubner and offer an explanation of the chemical regulatory device which they postulated."

The calorigenic property of epinephrin is the fine adjustment, and shivering is the coarse adjustment of the chemical regulation of temperature. One may well question the ultimate cooling value of ice cream soda water on a hot day.

The great adaptability of the cooling devices of the human body have been strikingly demonstrated in work done by Benedict, Mrs. Benedict, and Du Bois.[2] Hot dry air at a temperature of 80°C. was blown on the nude body of a man who, with the exception of his head, was enclosed in a bag. The air left the bag at a temperature of 45°. An hour of this treatment involved, in the case of Du Bois himself, a loss of body weight of 552 gm. as perspiration, an increase of mouth temperature from 36.6° to 37.1°, of pulse rate from 54 to 74 beats per minute, and of oxygen consumption from 252 c.c. per minute to 262 c.c. per minute, an increase of only 4 per cent. The efficiency of the human mechanism is here strikingly revealed. In an obese woman (weight, 105 kg.) the body loss through water evaporation was 660

[1] Cannon, W. B., Querido, A., Britton, S. W., and Bright, E. M.: Am. J. Physiol., 1926–27, **79**, 466.

[2] Benedict, C. G., Benedict, F. G., and Du Bois, E. F.: *Ibid.*, 1925, **73**, 429.

gm. per hour and the rectal temperature rose from 37.3° to 38.3°, the ill-conducting adipose tissue preventing the heat loss. The basal metabolism was not measured in this individual, but in two additional male subjects the metabolism increased 4 and 11 per cent. as the result of exposure to hot blasts of air. The skin temperatures which were normally 30° to 35° rose to between 35° and 41° in various parts of the body. It seems remarkable that the furnishing of hot blood to the subcutaneous area had so slight an effect on the basal metabolism as compared with that of a man normally situated in whom the skin is much cooler.

The effect of wind is such that an imperceptible air current may have a very pronounced influence. Rubner[1] has shown that wind becomes perceptible when it attains a velocity of 0.4 to 0.5 meter a second, and that if a wind much below this *threshold* value, having a velocity of 0.18 meter per second, act upon the exposed area of the arm, there is an increased heat loss of between 19 and 75 per cent., depending on the temperature of the wind, above what would be lost were the air quiet.

The effect of wind of moderate humidity and different temperatures on the metabolism of a man clad in summer clothes, as compared with the metabolism during atmospheric calm, is shown in Wolpert's[2] experiment below:

INFLUENCE OF WIND ON METABOLISM IN MAN

Temperature	Calm	Wind 1 Meter per Second	Wind 8 Meters per Second
	Grams CO_2 per Hour	Grams CO_2 per Hour	Grams CO_2 per Hour
2°	29.8		
10–15°	25.1	28.3	30.0
15–20°	24.1	....	30.1
20–25°	25.0	....	28.0
25–30°	25.3	22.2	24.4
30–35°	23.7	....	21.6
35–40°	21.2	22.2	22.1

According to this, a breeze having a temperature of 15° to 20° and moving at the rate of about 15 miles per hour (8 meters per second) has a greater effect upon the metabolism of a man clad in

[1] Rubner, M.: Arch. f. Hyg., 1904, **50,** 296.
[2] Wolpert, H.: *Ibid.*, 1898, **33,** 206.

summer clothing than a temperature of 2° would have during perfect atmospheric quiet. In all the experiments the smallest amount of carbon dioxid is eliminated between 30° and 40°.

The above experiments were performed on a thin man, and it will be noticed that there was no rise in his metabolism at a temperature of between 35° and 40°. Rubner explains this as due to the sufficiency of the evaporation of perspiration on the surface for the cooling of the organism.

A fat man, however, with a thick, ill-conducting layer of adipose tissue is not so immune to the effect of high temperatures upon his metabolism. This is especially pronounced in a damp climate. Thus Rubner[1] obtains the following results from a fat man wearing clothes:

INFLUENCE OF TEMPERATURE AND HUMIDITY ON THE METABOLISM OF A FAT MAN

Temperature	Humidity 30 Per Cent.		Humidity 60 Per Cent.	
	CO_2 in Grams per Hour	Grams H_2O Evaporated per Hour	CO_2 in Grams per Hour	Grams H_2O Evaporated per Hour
20°	33.7	56	30.7	17
28–30°	36.9*	134	44.5‡	170+ 31 g. sweat.
36–37°	42.6†	204 +14 g. sweat.	46.7§	186 +255 g. sweat.

* Body temperature rose 0.1°.
† Body temperature rose 0.0°.
‡ Body temperature rose 0.4°.
§ Body temperature rose 0.9°.

The fact that in the experiment where there was 30 per cent. humidity the metabolism largely increased at 36° to 37° without concomitant rise in body temperature leads Rubner to theorize that there must have been an overheating of the cells where the metabolism was progressing, even though this might not have been determinable by the clinical thermometer.

It appears that on a hot, humid day the metabolism of a fat individual may be 50 per cent. higher than on a day of moderate temperature and the same humidity. The whole of the body heat is lost through the evaporation of water which is here hindered by the

[1] Rubner, M.: "Energiegesetze," 1902, pp. 208, 232.

humidity. There is a large and exhausting excretion of sweat which on account of the difficulty in evaporation is not effective in cooling the body. At a moderate temperature, where the greater part of the heat loss is by radiation and conduction, the excretion of water is not excessive.

Lee[1] gives the following table which shows the influence of varying temperatures and humidities upon the body temperatures of a group of normal men:

Period of Confinement	20° C. 50 Per Cent. Humidity	23.9° C. 50 Per Cent. Humidity	30° C. 80 Per Cent. Humidity	30° C. 80 Per Cent. Humidity, with Fan Movement
8.30 A. M.	37.12° C.	36.83° C.	36.86° C.	36.98° C.
3.30 P. M.	36.52° C.	37.02° C.	37.28° C.	37.37° C.

There can be no doubt that climatic conditions modify racial characteristics. The emigrant from northern Europe, living upon a farm in the hot and often moist climate of an American summer, must restrict his layer of adipose tissue if he is to live comfortably. The same holds true in Italy. The difference between John Bull and Uncle Sam seems to be one of climatic adaptation. However the Scotsman is tall and lean. It is interesting to note that prostrations from the heat appear in New York with 66 per cent. humidity and a temperature of 31.5° (2.30 P. M., August 24, 1905). Rubner[2] says that a lightly clad thin man, at a temperature of 30° with humidity at 65 per cent., bore the effect so badly that he feared to raise the temperature to 35°. This individual had readily tolerated 35° in dry air. European emigrants to tropical countries tend to become thin.

The maximum mortality from "summer troubles" in children in New York coincides with the first great wave of heat accompanied by humidity which falls upon the city. Similar climatic conditions at later dates are not so mortal. It may be that the fatality of these intestinal affections is due to the inefficiency of the apparatus for the physical discharge of heat in the infant organism. It is also possible that infection may be more readily brought about under these conditions (p. 456).

Another factor in the heat regulation of man is clothes. Certain savage races living in cool climates do without clothes, as, for example,

[1] Lee, F. S., Edwards, D. J., *et al.*: Proc. Soc. Exper. Biol. and Med., 1914–15, **12**, 72.
[2] Rubner, M.: "Energiegesetze," 1902, p. 232.

aborigines of Terra del Fuego, who, according to the reports of travelers, substituted a covering of oil. In such races the process of "hardening" or the development of the physical regulation must be carried to a maximum. In civilized countries man endeavors to remove all the influence of chemical regulation by keeping his skin covered. Only about 20 per cent. of his surface is normally exposed to the air. The most important constituent of clothes is the air, which is a much worse conductor of heat than is the fiber. This is especially true of furs (p. 150). Thickness of the cloth will give a greater layer of air and will prevent heat loss from the body. A densely woven cloth prevents proper ventilation and does not absorb moisture. In hot weather a porous cloth next to the skin which can absorb moisture and permit its ready evaporation is of high importance. If a garment worn next to the skin becomes thoroughly wet the evaporation of sweat at a high temperature is largely prevented, to the great discomfort of the individual, while at a lower temperature heat loss through conduction is greatly facilitated, with a sensation of chill. Two experiments cited by Rubner[1] indicate the effect of clothes on metabolism. An individual was kept at a temperature of between 11° and 12° and wore different clothes at different times. His carbon dioxid and water excretion were as follows:

INFLUENCE OF CLOTHES ON METABOLISM IN MAN AT A TEMPERATURE OF 11° TO 12°

	CO_2 IN GRAMS PER HOUR	H_2O IN GRAMS PER HOUR	REMARKS
Summer clothes	28.4	58	Cold, occasional shivering.
Summer clothes and winter overcoat	26.9	50	Chilly part of the time.
Summer clothes and fur coat	23.6	63	Comfortably warm.

When the man was comfortable the chemical regulation of temperature was eliminated.

Rubner remarks that while the radiant energy of the sun is large in quantity, he has been unable to find any influence upon a man under ordinary circumstances, but believes that it may take the place of heat produced through chemical regulation on cold days. Thus a person living in the high altitude of Davos, Switzerland, feels much more comfortable in the sun on a cold day than he does in the shade.

[1] Rubner, M.: "Energiegesetze," 1902, p. 225.

However, Zuntz while living on the summit of Monte Rosa found that sunlight did not reduce metabolism (p. 585).

Hasselbalch[1] found that if the naked body of a man was strongly exposed to ultra-violet rays the rate of respiration was diminished while the depth was increased. The skin was red with dilated capillaries and the blood-pressure fell. Lindhard, in 1910, showed there is a yearly periodicity of the respiratory rate in the Arctic region, it being less in the spring and summer than in the winter. The enormous variations in the chemical intensity of the sun's rays in the Arctic region are undoubtedly the cause of this manifestation. Even in Copenhagen the same phenomenon has been observed by Hasselbalch and Lindhard.[2] The volume of respiration increases 26 per cent. in the summer. The intensity of the metabolic processes is not affected. This accords with the fact that there is no change in metabolism through an alteration of the respiratory rhythm induced by cutting the pulmonary branches of the vagus.[3]

It is reported[4] that a considerable reduction in the urinary nitrogen, creatinin and sulphur excretion occurs in dogs maintained with a constant protein diet when these are irradiated by artificial sunlight from a mercury vapor lamp.

Durig and Zuntz[5] find that the climate of the seashore does not influence the basal metabolism, nor does travel to the semi-tropical Canary Islands[6] nor the condition of sea-sickness.

COMPARATIVE METABOLISM OF DIFFERENT RACES

A number of comparative observations of the basal metabolism have been made upon various races of men, upon natives and emigrants, on Chinese living in New York, and on Europeans who have migrated to the tropics.

An outstanding contribution is that of Takahira[7] whose work has already been referred to. The following table presents results of an investigation concerning the basal metabolism of the Japanese:

[1] Hasselbalch, K. A.: Skan. Arch. Physiol., 1905, **17**, 431.
[2] Hasselbach, K. A., and Lindhard, J.: *Ibid.*, 1911, **25**, 361; Lindhard, J.: *Ibid.*, 1912, **26**, 221.
[3] Rauber, A., and Voit, C.: "Sitzungsber. der baeyerischen Akademie," 1868.
[4] Liebesny, P.: Z. physik. u. diät. Therap., 1920, **24**, 182.
[5] Durig, A., and Zuntz, N.: Biochem. Z., 1912, **39**, 422, 435.
[6] For an interesting discussion of the effects of tropical light on white men read C. E. Woodruff, "Medical Ethnology," New York, 1915.
[7] Takahira, H., Kitagawa, S., Ishibashi, E., and Kayano, S.: Abstract in English issued by Imperial Government Institute for Nutrition, Tokio, 1924, p. 41.

BASAL CALORIC REQUIREMENT OF JAPANESE

	Number	Average Age	Calories	
			In 24 Hr.	Per Sq. M. per Hr.
Males:				
Policemen	10	28	1474	38.88
Teachers	11	32.5	1338	36.17
Motormen and car conductors	11	31	1373	36.92
Barbers	9	34	1299	36.62
Skilled laborers	9	32	1331	36.99
Scholars and office workers	10	31	1392	36.76
Laborers	7	34	1463	39.48
Merchants	6	35	1235	36.48
Total	73		Average	37.30
Females:				
Teachers	16	34	1043	31.46
Stenographers	16	21	1100	34.68
Laborers	11	37	1068	35.14
Total	43		Average	33.88

The figures average below those of Du Bois (see p. 139).

Takahira notes that there are individual variations due to mode of life, occupation, and physical training. In women, whose basal metabolism averaged 9 per cent. below that of men, determinations during the menstrual period were avoided, but no rise in metabolism took place before the period (see p. 526).

The basal metabolism of common laborers was higher than that of those in other occupations:

	Calories per Sq. M. per Hr.	Increase above Japanese Standard Per Cent.
30 common laborers (men)	40.23	+7.2
20 " " (women)	36.43	+7.2

Takahira concludes that the differences in metabolism between Japanese, Europeans, and Americans are slight and are such as may be observed in groups of any race.

These conclusions are supported by the observations of Okada, Sakurai, and Kameda[1] who find that 42 Japanese men show a basal metabolism which is 2 per cent. less than the Du Bois standards and that 11 women were 0.7 per cent. less than that standard.

Eijkman[2] took a Zuntz portable respiration apparatus to the tropics and in investigations made at Batavia in Java found that the

[1] Okada, S., Sakurai, E., and Kameda, T.: Arch. Int. Med., 1926, **38**, 590.

[2] Eijkman, C.: Pflüger's Arch. gesam. Physiol., 1896, **64**, 57; Virchow's Arch. path. Anat. u. Physiol., 1895, **140**, 125.

basal heat production in the tropics was the same as in the temperate zone. He made the important observation that native Malays perspired less than Europeans living in Java and lost 14 per cent. more of their heat by conduction than the Europeans. Only when drinking water in quantities unusual for them did they sweat like Europeans. Exposed to the sun, the skin of the Malay sweats earlier than the skin of the white man.[1] With the outbreak of sweat the skin surface cools.

An excellent report of metabolism in the tropics is given by Knipping,[2] who took a trip around the world in 1922. He carried a Benedict respiration apparatus with him and made observations, some on board ship, some in Batavia, others in Borneo and in other tropical regions. He notes that in the tropics the nude body of the laborer is covered with a film of sweat, the evaporation of which carries off most of the heat produced. The European in the tropics drinks more water (sometimes whisky and soda), perspires more and also less effectively, losing sodium chlorid thereby, which loss, it is said, leads ultimately to a destruction of red blood cells and to the production of tropical anemia.

Some of Knipping's observations have been tabulated in the table given on p. 167.

Colombo is in Ceylon; Batavia is in Java; Padang in Sumatra; and Makassar, Celebes, and Surabaya are in other islands of the Dutch East Indies.

In this table the average level of the basal metabolism of Europeans migrating to the tropics underwent no change. Knipping finds that there often is an increase of about 5 per cent. Body temperature records were not taken or one might attribute the slight rise in basal metabolism to an increase in body temperature. The three Europeans quoted as having lived long in the tropics showed a reduction in metabolism equal to 5 per cent. according to the Harris-Benedict prediction standards. This may be due to the tendency of Europeans living in the tropics to grow thin. The average of six natives, Malay and Chinese, shows a decrease of 2.5 per cent. from the prediction standard. Evidently life at the equator has the same basal metabolism as in temperate climes. All this is not surprising, for our stock presumably arose in tropical waters many millions of

[1] Aron, H.: Philippine J. Sc., 1911, B, **6**, 100.
[2] Knipping, H. W.: Z. f. Biol., 1923, **78**, 259.

years ago, and we have preserved our heritage. In the future the same level of basal metabolism may be established for man in a laboratory at the North Pole.

EFFECT OF TROPICAL CLIMATE ON THE BASAL METABOLISM

Race	Age	Wt.	Time in the Tropics	Address with Latitude		Metabolism			
				Home	Tropics	Benedict Prediction Tables	Home	Tropics	Temp. in Tropics
	Yrs.	Kg.							°C.
European	22	59	2½ weeks	Rotterdam 52°	Colombo 7°	1605	1585	1642	28
"	20	67.5	3½ months	Antwerp 51°	Colombo	1742	1769	1947	28
"	18	64	3½ "	Bremen 53°	Padang 1°	1686	1670	1450	31
"	25	60	3 "	Bremen	Makassar 5°	1514	1526	1446	31
"	29	75	1 "	Rotterdam	Colombo	1813	1848	1932	28
"	30	62	12 years	.....	Makassar	1537	....	1355	30
	37	70.5	10 "	.....	"	1667	....	1596	30
	35	66	2 "	.....	Surabaya 7°	1613	....	1612	31
Malay	25	48	Native	.....	Surabaya	1359	....	1267	28
Chinese	20	56	"	.....	Celebes 2°	1528	....	1477	27
"	35	60	"	.....	Celebes	1446	....	1414	29
Malay,*	22	58	"	.....	Batavia 6°	1516	....	1458	29
"*	25	53	"	.....	Batavia	1457	....	1483	29
"*	28	51	"	.....	Surabaya	1331	....	1323	30

* Patients with beri-beri.

Experiments made at Beirut, Syria, by Turner[1] upon the racial factor show no marked differences of metabolism in representatives of the medley of races included in the following table:

THE RACIAL FACTOR IN BASAL METABOLISM
(Basal metabolism of the medical and nursing schools at Beirut)

	No.	Men	Women
Americans	13	−0.48 per cent.	
Armenians	..	−1.14 per cent.	−2.3 per cent.
Jewesses, Syrians, Palestinians and Egyptians	2 ..	.....	−5.9 per cent.
Palestinians, Syrians, Persians, Iraquians, Transjordanians	..	−3.0 per cent.	
Egyptians	15	−6.5 per cent.	

[1] Turner, E. L.: J. Am. Med. Assn., 1926, **87**, 2052.

The results reported are not all on the same key and the other side must be presented. Thus, de Almeida,[1] working in the Brazilian tropics, reports that the basal metabolism is reduced 24 per cent. below the normal. Sundstroem,[2] who has written an excellent review on the "Physiological Effects of Tropical Climate,"[3] states that in tropical North Queensland the basal metabolism of males averages 22 per cent. and of females 25 per cent. below the normal, although physically active individuals show a higher standard.

Mac Leod, Crofts, and Benedict[4] investigated the basal metabolism of 9 oriental college women living under the supposed superstimulating conditions of American life and found them to be 10 per cent. below the normal as given for women by Du Bois and by Benedict.

According to Hafkesbring and Borgstrom[5] the basal metabolism of whites living in semi-tropical New Orleans is −18 per cent. (Du Bois) and −16 per cent. (Harris-Benedict). In New Orleans the protein intake is low, 60 per cent. of the Northern intake, but the calories taken are the same.

It is stated that, as the result of exposure to the light of quartz mercury vapor lamps sufficient to cause marked pigmentation on the chest and back, the basal metabolism usually falls.[6] This may have a bearing on tropical metabolism (see pp. 142, 507).

It may be added that a Filippino student of small size, working in our own laboratory among our Cornell students, manifested a metabolism in conformity with the normal average of his fellow-students.[7] On the basis of the whole of the evidence it does not appear wise to state that the influence of race or of a tropical climate may greatly reduce the basal metabolism. Rather must one remember that the standards of metabolism are devised for well-nourished people in good health, capable of doing a day's work, and who are in the habit of taking a mixed diet. Undernutrition as a factor by itself may reduce basal metabolism one-third, and this must always be vividly borne in mind.

The fundamental heat production in the organism is not reduced by liberating heat from electric energy within the organism.[8] Thus,

[1] de Almeida, A. O.: J. Physiol. et Path. gen., 1919–20, **18,** 713; 958.
[2] Sundstroem, E. S.: Univ. of California Pub. in Physiol., 1926, **6,** 123.
[3] Sundstroem, E. S.: Physiol. Rev., 1927, **7,** 320.
[4] Mac Leod, G., Crofts, E. E., and Benedict, F. G.: Am. J. Physiol., 1925, **73,** 449.
[5] Hafkesbring, R., and Borgstrom, P.: *Ibid.*, 1926–27, **79,** 221.
[6] Mason, E. H., and Mason, H. H.: Arch. Int. Med., 1927, **39,** 317.
[7] Bassett, S. H., Holt, E., and Santos, F. O.: Am. J. Physiol., 1922, **60,** 574.
[8] Durig, A., and Grau, A.: Biochem. Z., 1912–13, **48,** 480.

although high frequency currents equal to 1.8 amperes and 176 volts were passed through the body during two and one-half hours under conditions such as avoided high concentration, and though heat was produced thereby which was equal to three to four times the energy requirement of the time, yet there was in fact a slight increase in the oxidative processes of the subjects attributable to hyperthermia, sweating, increased pulse, and respiratory activity. Extraneous heat, therefore, will not replace the chemical energy of the food-stuffs in maintaining the life processes.

In what follows it will be shown that the ingestion of food may add to the heat production of the organism and diminish the necessity of heat production through chemical regulation in cold weather. Also it may very uncomfortably increase the production of heat and perspiration in warm weather, especially if protein be largely taken (p. 284).

From this chapter the influence of climate is seen to be noteworthy. It explains why a temperature of $-40°$ may be comfortably borne in winter, in the Adirondack Mountains, for example, if the air be dry and still; why a much warmer atmosphere which is damp and windy may "cut to the bone" with cold; why a hot, dry climate may be entirely comfortable, when air at the same temperature laden with moisture may strike down many fatally and oppress every one; and how the effect of heat may be modified by the breezes and baths at the seashore. It does not explain the effect of the dry sirocco wind which blows from the Desert of Sahara, the universal depressant action of which has been attributed to unknown cosmic influences.

CHAPTER VII

THE CONSTANCY OF THE BASAL METABOLISM AND THE EFFECT OF UNDERNUTRITION UPON IT

Think, reader, for thyself, so God allow
Thee profit from thy reading, think I say . . .—DANTE.

ZUNTZ,[1] who first devised the proper technic of basal metabolism, has left us this record of his own:

METABOLISM OF ZUNTZ

YEAR	AGE	WEIGHT	O_2 CC. PER MINUTE	CALORIES PER SQUARE METER (MEEH) PER DAY
		Kg.		
1888	41	65.7	236	804
1901	54	67.6	231	780
1903	56	67.6	228	773
1910	63	68.5	235	792
1916	69	60.6	198	709
1917	70	59.4	198	723

Only on account of undernutrition due to war conditions was there a fall in basal metabolism in 1916 and 1917.

BASAL METABOLISM OF E. F. D. B.
(Height, 178–178.8 cm.)

DATE	AGE	WT.	SURFACE HT.-WT.	CALORIES		PERCENTAGE VARIATION FROM AVERAGE
				PER HOUR	PER SQ. M. PER HR.	
	Yrs.	Kg.	Sq. M.			
May 17, 1913	30	75.5	1.95	73.2	38.1	+2.1
Mar. 30, 1914	31	74.3	1.93	74.1	38.4	+2.9
May 18, 1914	31	73.7	1.92	71.3	37.2	−0.3
May 6, 1915	32	74.6	1.93	71.8	37.2	−0.3
May 7, 1915	32	74.2	1.93	68.6	35.5	−4.8
Apr. 12, 1916	33	76.5	1.94	75.4	38.8	+4.0
Apr. 25, 1916	33	77.3	1.95	73.2	37.5	+0.5
Dec. 18, 1916	34	73.9	1.90	76.2	40.1	+7.2
May 10, 1922	39	78.0	1.97	68.6	34.8	−6.7
Oct. 7, 1923	41	74.7	1.93	70.8	36.7	−1.6
Apr. 10, 1924	..	75.0	1.94	71.7	37.0	−0.8
Apr. 7, 1927	44	75.7	1.93	70.1	36.3	−2.9
Average	..	....	....	....	37.3	±2.8

[1] Zuntz, N., and Loewy, A.: Berliner klin. Wochenschr., 1916, **53**, 825; Biochem. Z., 1918, **90**, 244.

The record of the basal metabolism of Du Bois, which extends over a period of 14 years, is here brought up to date.

It is evident that the expense in energy of running the resting human machine is remarkably constant. The maximum variations are 7.2 per cent. above and 6.7 per cent. below the average normal of the individual.

In the dog the constancy of the basal metabolism may be quite extraordinary. This is because (1) a constant diet may be administered; (2) the animal may be confined in a cage for a long period of time, which "cage life," in reducing muscular vigor, lowers metabolism; (3) emotional reactions are absent. The following experiments are upon a dog which lived in the laboratory under the experimental conditions above stated:[1]

THE BASAL METABOLISM OF DOG XIX (WEIGHT 11.5 KILOS) DURING 1923–24

Experiment No.	Date	R. Q.	Calories per Hr.	
			Indirect	Direct
	1923			
96	Jan. 30	0.83	16.58	17.08
102	Feb. 14	0.82	16.42	15.98
107	" 21	0.80	16.44	16.34
110	Mar. 2	0.81	16.13	17.46
115	" 13	0.79	16.76	18.01
122	" 24	0.80	16.46	16.60
129	Apr. 4	0.88	16.52	17.02
146	Mar 9	0.83	16.74	14.26
Average for 1923		**0.82**	**16.51**	**16.72**
167	Dec. 5	0.79	16.39	15.92
	1924			
175	Mar. 6	0.81	16.43	15.71
181	" 27	0.88	16.57	16.01
185	Apr. 3	0.84	16.99	14.40
190	" 8	0.89	16.78	16.52
196	" 24	0.89	16.03	
Average for 1923–24		**0.85**	**16.53**	**15.71**
" " 15 mos.		**0.83**	**16.52**	**16.21**

In these experiments the maximum variation in the basal metabolism did not exceed ±2.9 per cent. of the average during a period of 15 months. The oxygen consumption of an alcohol flame burning in the calorimeter in frequent tests of the apparatus for accuracy

[1] Rapport, D.: J. Biol. Chem., 1924, 60, 497.

showed, during the same period, errors of ± 1.9 per cent. *The basal metabolism of the dog was therefore, for a period of* 15 *months, nearly as uniform as was the apparatus with which it was measured.*

ALCOHOL CHECKS

Experiment No.	Date	R. Q.	Calories per Hr.		Difference
			Indirect*	Direct	
	1923				Cals.
168	Jan. 4	0.663	25.15	23.45	−1.70
169	" 5	0.672	27.16	27.94	+0.78
170	" 20	0.678	25.10	25.42	+0.32
171	" 25	0.662	30.54	31.03	+0.49
172	Mar. 9	0.668	25.75	26.08	+0.33
173	May 3	0.659	24.90	25.42	+0.52
174	" 11	0.670	23.42	23.35	−0.07
175	" 22	0.666	21.65	22.37	+0.72
Average		0.667	25.46	25.63	+0.17

* Calculated upon the CO_2.
Maximal O_2 error = −1.86 per cent. (Experiment 170).
" " " = +1.15 " " (" 173).

Not only this, but Rapport and Beard[1] have recently pointed out that two dogs of the same size may have exactly the same metabolism when food, exercise, and method of handling are the same. Working in Cleveland, Ohio, on one dog, they duplicated the results which Plummer, Deuel, and Lusk[2] obtained with another dog in New York. These results are as follows:

	Dog of Plummer, Deuel, and Lusk	Dog of Rapport and Beard
Wt. in kg	6.5	6.5
R. Q.	0.87	0.85
Cals. per hr	12.73	12.40

Dogs of similar weight and form have exactly the same basal metabolism. It is well to remember the constancy of this background of basal metabolism, for on it has been built a superstructure which has given valuable information.

UNDERNUTRITION

An influence which profoundly reduces metabolism is undernutrition. In commenting on the reduction in metabolism of Bene-

[1] Rapport, D., and Beard, H. H.: J. Biol. Chem., 1927, **73**, 285.
[2] Plummer, N. H., Deuel, H. J., Jr., and Lusk, G.: *Ibid.*, 1926, **69**, 339.

dict's fasting man in the last (1917) edition of this book, the statement was made that there appeared to be a specific reduction in metabolism coincident with undernutrition. Events since then have abundantly verified this statement. The influence of undernutrition will be considered again, especially in the chapter on diabetes (see p. 675).

During the World War, Benedict and his associates[1] took up the subject of determining the basal metabolism of healthy young men whose weight was being reduced by administering a diet containing some good animal protein but decidedly deficient in caloric value. Benedict's group of men in Squad B were suddenly reduced from a caloric intake of 4000 calories per day to one of 1375 net available calories daily. For three weeks this group of 12 men partook of this diet, which contained 8.21 gm. of N. The N output in the urine and feces averaged 11.29 gm. per person per day. Therefore a daily loss of body N of 3.1 gm. took place, or 65 gm. in 3 weeks. Since 1 kg. of body weight of a well nourished man contains 30 gm. N and the average weight of these young men was 67.9 kg., it follows that their bodies contained 2037 gm. at the start. A loss of 65 gm. of body N means a loss of only 3.2 per cent. of the original total.

Lusk[2] has elsewhere analyzed the results of Benedict, rearranging his data. The essentials are found in the following table:

	During Normal Diet	After 3 Weeks of 1375 Cals.	Per Cent. Reduction
Basal metabolism in calories per day	1745.0	1293.0	32.0
Calories per kg. per day	25.7	20.4	20.0
Calories per sq. m. body surface per day	872.0	647.0	27.0
Body weight in kg	67.9	63.4	6.5
Body N in gm	2037.0	1972.0	3.2

This table demonstrates that the loss of a paltry 65 gm. of body N, or 3.2 per cent. of the whole, bears no relation to the great fall in basal metabolism of 27 per cent. per square meter of body surface. So there appears here not only a mechanism of N minimum protecting life from destruction, but also a biological adaptation to a lowered energy intake preventing the exhaustion of the reserve of body fat.

[1] Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M.: Carnegie Institution of Washington, Pub. 280, 1919.

[2] Lusk, G.: Physiol. Rev., 1921, 1, 523.

One can compare the results obtained with the results calculated by Lusk for Benedict's fasting man (see p. 101):

	Benedict's Fasting Man	Benedict's Undernourished Squad B
Percentage reduction in basal metabolism	29	32
Loss of body N in gm	277	65
Percentage loss of body N	16	3
Percentage loss of body weight	20	6.5

One cannot trace the cause of lowered metabolism in undernutrition to a reduction of the mass of body protein nor to a reduction in the mass of body substance itself. It exists in an innate protective mechanism, the nature of which one can only dimly surmise.

The young men so nourished lacked physical strength and lacked a sense of well-being.

CHAPTER VIII

OXIDATION AND REDUCTION

The cell is in fact not a single room in which all the chemical processes occur in a higgledy-piggledy manner as they occur in a beaker glass, but it is rather a well organized chemical factory with different chemical processes occurring in different regions and in which substances are being elaborated as fast as they are required.—A. P. Mathews.

Those acquainted with the fundamental laws of general metabolism know that enzymes, be they hydrolytic, oxidative, or proteolytic, are not the masters but the servants of the living cells. On no other basis can one explain the constancy of the basal metabolism, its demonstrated relation to surface area, its similar value in different animals of the same size and weight, or the identity of the quantum of energy necessary to accomplish a given amount of mechanical work. On no other conception is the minimal value of protein metabolism comprehensible when a carbohydrate diet is taken.

For each trifling reaction in the scheme of alcoholic fermentation presented by Neuberg the existence of a specific ferment is assumed; for example carboxylase, which splits pyruvic acid into acetaldehyd and carbonic acid. Kostytschew[1] cannot believe in the existence of the long line of ferments postulated by Neuberg.[2]

There is a general rule that oxygen does not attack organic substances dissolved in water at the temperature of the blood and at a pH of 7. An exception to this, however, was found by Warburg and Yabusoe,[3] who directly oxidized fructose in a neutral phosphate solution by means of molecular oxygen. Glucose is completely resistant to such treatment.

Dakin[4] has stated that the laboratory oxidation of biological substances with peroxide of hydrogen gives results which are closely akin to those effected by the living cell. He cites the following examples:

[1] Kostytschew, S.: Z. physiol. Chem., 1926–27, **162**, 139.
[2] Neuberg, C.: *Ibid.*, 1926, **157**, 299.
[3] Warburg, O., and Yabusoe, M.: Biochem. Z., 1924, **146**, 380.
[4] Dakin, H. D.: "Oxidations and Reductions in the Animal Body," 2d ed., London and New York, etc., 1922, p. 10.

$$CH_3—CH_2—CH_2—COOH \rightarrow CH_3—CO—CH_2COOH$$
Butyric acid — Beta-keto-butyric acid

$$CH_3—CHOH—CH_2COOH \rightarrow CH_3—CO—CH_2COOH$$
Beta-hydroxybutyric acid — Aceto-acetic acid

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH—CH_2—CHNH_2—COOH \rightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH—CH_2—COOH + NH_3 + CO_2 + H_2O$$
Leucin — Isovaleric acid

$$CH_2OH—CHOH—CH_2OH \rightarrow \begin{matrix}CH_2OH—CHOH—CHO\\ \text{Glyceric aldehyd}\\ CH_2OH—CO—CH_2OH\\ \text{Dioxyaceton}\end{matrix}$$
Glycerol

One must remember, however, as a fundamental fact, that if peroxide of hydrogen is produced in a living cell, its quantity is dependent on the requirement of that cell for oxygen. The machinery of the living cell is the dominant reigning force, not peroxide of hydrogen running riot.

This warning is needed because many modern workers have neglected the background of the energy metabolism, a knowledge of which is necessary for the full interpretation of their labors. It is uttered in no disparagement of their work, which is in the highest degree interesting and stimulating.

At the present time there are two dominant theories with regard to the mechanics of cell oxidation, that of Wieland[1] and that of Warburg.[2] *The theory of Wieland* is accepted by Thunberg,[3] Ahlgren,[4] and by Sir Gowland Hopkins.[5] Wieland's theory is that all oxidations are effected through the withdrawal of hydrogen from organic compounds. This is accomplished through *dehydrases*. The hydrogen so withdrawn is then oxidized in combination with a suitable acceptor. If molecular oxygen is the acceptor, then H_2O_2 is produced. *Catalase* is able to dissociate this peroxide of hydrogen into water and molecular oxygen, thereby protecting the tissue. Or, the oxygen liberated may react with hydrogen, which is freed from organic substances, and be converted into water. These formulae illustrate the reactions.

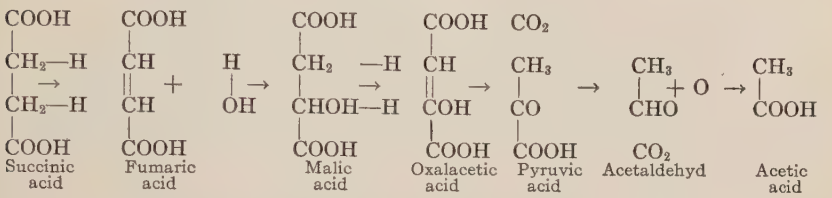
$$\begin{matrix}O & H\\ \| & \\ O & H\end{matrix} + \quad = H—O—O—H$$

$$H—O—O—H + H_2 = 2H_2O$$

[1] Wieland, H.: Ber. d. deut. chem. Ges., 1914, **47,** 2085; Ergeb. d. Physiol., 1922, **20,** 477.
[2] Warburg, O.: Festschr. Kaiser Wilhelm Ges., 1921, 224.
[3] Thunberg, T.: Skan. Arch. Physiol., 1918, **35,** 163.
[4] Ahlgren, G.: *Ibid.*, 1921, **41,** 1; 1925, **47,** Suppl.
[5] Hopkins, F. G.: *Ibid.*, 1926, **49,** 33.

Wieland's theory therefore depends upon the activation of hydrogen and its subsequent oxidation.

The entrance of oxygen into an organic complex after the withdrawal of hydrogen may be accomplished through hydrolysis. The phenomenon is represented as follows:



Two of the reactions show the process of decarboxylation, or loss of carbonic acid.

A classical example of a hydrogen acceptor is methylene blue. It "accepts" hydrogen and is converted into methylene white. This happens when it is brought into contact with tissue. This has been shown especially by Thunberg[1] and his pupils. Battelli and Stern[2] first showed that succinic acid, which is highly resistant to oxidation in the air, is readily converted into malic acid by the tissues. Thunberg and also Einbeck[3] discovered that the first product formed is fumaric acid. For if finely cut frog's tissue be washed with water it no longer reduces methylene blue, but if succinic acid be added, then fumaric acid and later malic acid are abundantly produced. Dehydrogenation of succinic acid is brought about and hydrogen is "donated" to the methylene blue. The solution bleaches due to the formation of methylene white. In the language of Thunberg a "succino-dehydrogenase" which is also a "hydrogentransportase" is responsible for removing $_2H$ from succinic acid and conveying it to methylene blue. Sugar, fat, and amino-acids early undergo dehydrogenation accompanied by decarboxylation. Hydrogen either unites with oxygen, forming peroxide, or it reduces other substances. All foods are hydrogen donators under this scheme and at bottom hydrogen may be considered the common fuel of all cells.

At times an aldehyd like acetaldehyd may accept hydrogen and be reduced to an alcohol, as in the reaction

$$CH_3—CHO + H_2 = CH_3CH_2OH$$

[1] Thunberg, T.: Skan. Arch. Physiol., 1918, **35,** 163.
[2] Battelli, F., and Stern, L.: Biochem. Z., 1911, **30,** 172; *Ibid.*, **31,** 478.
[3] Einbeck, H.: Z. physiol. Chem., 1914, **90,** 301; Biochem. Z., 1919, **95,** 296.

Or it may be that such a body as acetaldehyd may undergo hydrolysis and then be converted into acetic acid by dehydrogenation:

$$CH_3CHO + H_2O \rightarrow CH_3{-}CH\begin{matrix}OH\\OH\end{matrix} \rightarrow CH_3COOH + H_2$$

These are essential conceptions in Wieland's theory.

Another illustration of the entrance of water into an organic complex, a reaction which is probably largely concerned with carbohydrate metabolism, is the transformation of methylglyoxal into lactic acid by the well-known internal Carnizzaro reaction (see p. 232):

$$\begin{array}{lcl} CH_3 & \rightarrow & CH_3 \\ | & & | \\ CO + H_2 & & CHOH \\ | & & | \\ CHO\ \ O & & COOH \end{array}$$

It would seem as though this theory of Wieland could be brought into harmony with the known facts concerning biological oxidations by assuming that the activity of the mechanism is proportional to the requirements of the cell.

The *theory of Warburg* involves the direct production of activated oxygen, through the conversion of bivalent oxide of iron into peroxide of iron, and the dissociation of the latter. Warburg denies that H_2O_2 ever arises biologically and affirms that activated oxygen is the cause of oxidation. Warburg's respiration model consists of blood charcoal suspended in water. If this be shaken with oxygen alone there is no effect. If cystin in neutral, acid, or alkaline solution is shaken with oxygen, there is no oxidation. But if the system charcoal, cystin and oxygen, be used a very rapid oxidation takes place with the production of CO_2, NH_3, and H_2SO_4.[1] Warburg has further found that his charcoal model oxidizes glycin, alanin, and other amino-acids on the surface of the charcoal with the production of CO_2, NH_3, and aldehyds. The iron in the blood charcoal acts as the catalytic agent.

As an illustration of the profound effect of the presence of iron the acceleration of the oxidation of cystein to cystin may be mentioned. The spontaneous oxidation of cystein to cystin was first discovered by Mathews.[2] Abderhalden[3] states that, though iron is not neces-

[1] Warburg, O., and Negelein, E.: Biochem. Z., 1921, **113**, 257.
[2] Mathews, A. P., and Walker, S.: J. Biol. Chem., 1909, **6**, 21, 29.
[3] Abderhalden, E., and Wertheimer, E.: Pflüger's Arch. gesam. Physiol., 1923, **198**, 122.

sary in this reaction, yet it promotes it greatly, and Warburg and Sakuma[1] have shown that, whereas shaking 20 mg. of their purest preparation of cystein hydrochlorid in 10 cc. of water at 20° C. and with a C_H of $(10^{-7.7})$ resulted in the utilization of 1 cmm. O_2 per hour, the addition of $\frac{1}{10{,}000}$ gm. Fe in the form of chlorid increased the oxidation process to correspond to a utilization of 9 cmm. of O_2 per hour. Warburg estimates that 1 mg. of Fe in the presence of cystein may cause 1700 cmm. of O_2 to be used per minute. It is a metal catalysis. The reaction involved is as follows:

$$\begin{array}{l} CH_2SH \\ | \\ CHNH_2 \\ | \\ COOH \\ \text{Cystein} \end{array} + \tfrac{1}{2}O = \begin{array}{l} CH_2S— \\ | \\ CHNH_2 \\ | \\ COOH \\ \text{Cystin} \end{array} + \tfrac{1}{2}H_2O$$

Oppenheimer,[2] in an exhaustive review of the whole subject, comes to the conclusion that the conception of Warburg is not an acceptable theory of vital oxidation. He says it is not all that Warburg thinks it is. Its limitation to the catalysis of oxygen by iron rules it out. It cannot be harmonized with the dehydrogenizing mechanism which is effective in the absence of oxygen.

Hopkins, in his notable address "On Current Views Concerning the Mechanisms of Biological Oxidation," delivered at the opening of the XIIth International Physiological Congress held at Stockholm, 1926, refers to the work of Toda,[3] who showed that, if pure cystein hydrochlorid is brought into contact with methylene blue, cystein is oxidized through withdrawal of hydrogen to the hydrogen acceptor, and the methylene blue becomes methylene white:

$$\underset{\text{Cystein}}{2R—H} + \underset{\text{Methylene blue}}{M} = \underset{\text{Cystin}}{2R} + \underset{\text{Methylene white}}{MH}$$

The reagents were purified from iron, and it required 300 minutes to effect the bleaching. However, the addition of a trace of ferrous sulphate caused the reaction to be completed in 7 minutes. Here, apparently, hydrogen and not oxygen was activated by iron. Hopkins suggests that iron acts in some way on the thiol group of the cystein, promoting its donation of hydrogen either to methylene blue

[1] Warburg, O., and Sakuma, S.: Pflüger's Arch. gesam. Physiol., 1923, **200,** 203.
[2] Oppenheimer, C.: "Die Fermente und ihre Wirkungen," 5th ed., Leipzig, 1926, **2,** 1254.
[3] Toda, S.: Biochem. Z., 1926, **172,** 34.

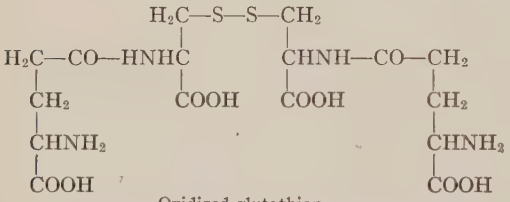
under anaerobic conditions, or to oxygen with the production of peroxide of hydrogen under aerobic conditions.

It may be added that Meyerhof[1] has found that thioglycollic acid, like cystein, may act as an auto-oxidizing system.

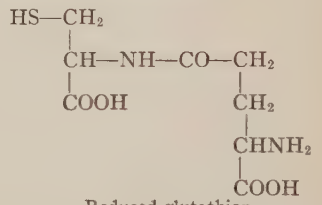
As to experimental work on the subject of oxidation, it is wise to consider the warning of Abderhalden.[2] "We do not wish to minimize the importance of the experiments of Warburg. He has suggested possibilities which might indeed take place in life. But we are far from a clear idea of oxidation processes in the cell which is actually founded upon established facts. In the interim we deal mainly with hypotheses."

GLUTATHION

One of the most brilliant discoveries of recent years is that of glutathion by Hopkins.[3] It is an auto-oxidizable constituent of the cell, forming a thermostable oxidation-reduction system. It has been synthetically produced and has the following formula:[4]



Oxidized glutathion



Reduced glutathion

The reduced compound is a normal constituent of the tissues of animals and of plants, while oxidized glutathion is present only in very small quantities. Rabbit's muscle contains 0.04 and liver 0.24 per cent.[5] of glutathion; yeast contains 0.2 per cent. Twenty grams have been obtained from 50 kg. of moist compressed yeast.

Hopkins and Dixon[6] described reduced glutathion as a dipeptid containing glutamic acid and cystein, and oxidized glutathion as an association of four amino-acids in which the groupings $-\overset{SH}{SH}$ became —S—S—. The oxidation of reduced glutathion was thus accomplished:

$$\begin{matrix} -SH \\ \\ -SH \end{matrix} + O_2 = -S-S- + H_2O_2.$$

[1] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1923, **149,** 531.
[2] Abderhalden, E., and Wertheimer, E.: *Ibid.*, 1923, **200,** 649.
[3] Hopkins, F. G.: Biochem. J., 1921, **15,** 286.
[4] Stewart, C. P., and Tunnicliffe, H. E.: *Ibid.*, 1925, **19,** 207.
[5] Tunnicliffe, H. E.: *Ibid.*, p. 194.
[6] Hopkins, F. G., and Dixon, M. J.: J. Biol. Chem., 1922, **54,** 527.

In this fashion reduced glutathion becomes a hydrogen donator to molecular oxygen, which plays the rôle of hydrogen acceptor. The oxidized glutathion G—S—S—G now is in a position to renew its rôle as hydrogen acceptor in accordance with the theory of Wieland. Reduced glutathion is not only readily oxidized by molecular oxygen but it donates its hydrogen to methylene blue. Factors in the tissue, by donating hydrogen, readily reduce the oxidized compound. A continuous transfer of hydrogen is thus established.

Glutathion is readily soluble in water. Chopped muscle, thoroughly washed in cold water, may be repeatedly extracted with boiling water, then dehydrated with alcohol, dried *in vacuo*, and ground to a fine powder without losing its power to reduce added glutathion. If 10 mg. of oxidized glutathion be added to a gram of tissue, prepared as above and placed in a phosphate buffer solution with a pH between 7 and 8, the system continually "respires," absorbing oxygen and giving off carbon dioxid. During the earlier stages the respiratory quotient is unity, indicating an oxidation of carbohydrate induced through a mechanism which primarily withdraws hydrogen from the tissues. The hydrogen is oxidized, the tissues undergo hydrolysis, and CO_2 cleavage takes place. The reaction is greatly slowed by increasing the acidity of the buffer solution.[1]

Quastel[2] publishes from Hopkins' laboratory an important analysis of the mechanism of oxidation and reduction *in vivo*. He comes to the conclusion that the site of the reduction of methylene blue and also the site of the activation of the substrate molecule is at the cell surface. He finds no evidence in the filtrates of the media, or in the washings of bacteria which show the existence of the "hydrogen transportases" which are soluble reducing enzymes according to Thunberg. He states that the cell surface may have a complicated "geography," perhaps an irregularity of distribution of groups of molecules. Hence there may be locally intense electric fields, though the average for the whole surface may be very weak. Hardy and Harvey[3] incline to the idea that the total surface charge varies with the state of activity of the living cell. Quastel suggests that the activation of a molecule is due to the application of an external electric field. He quotes the remarks of Sir J. J. Thomson[4]

[1] Tunnicliffe, H. E.: Biochem. J., 1925, **19**, 199.
[2] Quastel, J. H.: *Ibid.*, 1926, **20**, 166.
[3] Hardy, W. B., and Harvey, H. W.: Proc. Royal Soc. (London), 1911, B, **84**, 217; Zentralbl. f. Physiol., 1911, **25**, 1125.
[4] Thomson, J. J.: Nature, 1923, **112**, 826.

regarding the effect of an external electric field upon unsaturated linkages:

"Suppose that there is a double bond between two carbon atoms $C_2 = C_1$, the octets of electrons around C_1 and C_2 having four electrons in common situated between C_1 and C_2. If an external electric field acts on the molecule, tending to make electrons move from left to right, some of the electrons held in common may be so far displaced from C_2 towards C_1 that they can no longer be regarded as shared with C_2. If two of these are displaced far enough for this to happen, the octet around C_1 will be intact and C_1 will be saturated, whilst the octet around C_2 will be reduced to a sextet, so that C_2 will be unsaturated and chemically active: there are still two electrons left between C_1 and C_2 to form a single bond binding C_1 and C_2 together."

The same force which causes a shift in the electrons will cause a shift in the protons (H-ions). The reactions may be thus recorded:

—CH=CH—	—C̆—CH$_2$—
—CH=O	—C̆—OH
—CH=N—	—C̆—NH—
Normal forms	Activated forms

The effect of a carboxyl group is to produce an electric field at the alpha-atom which attracts positive electricity. This is so much stronger on the alpha-C atom than on the beta-C that there is a shift of the proton from one to the other, leaving the beta-carbon chemically unsaturated. This appears as follows:

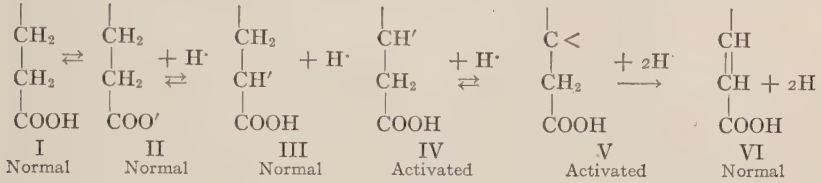
A—CH=CH COOH	A—C̆—CH$_2$—COOH
A—CH=CH—CH$_3$	A—CH$_2$—C̆—CH$_3$
A—CH=CH—CH$_2$—COOH	A—CH$_2$—C̆—CH$_2$COOH

Another influence of the proximity of the —COOH radicle to the activated carbon is that activated fumaric acid attracts hydrogen (positive electricity), whereas if a CH_3 group be near the activated carbon as in crotonic acid, the unsaturated C-atom has a strong attractive effect for negative electricity and is converted into aceto acetic acid. Hence fumaric acid is a powerful hydrogen acceptor and crotonic acid is not.

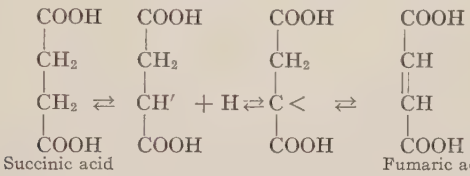
COOH—CH = CH—COOH → COOH—C̆—CH$_2$—COOH →
Fumaric acid, normal form
COOH—CH$_2$—CH$_2$—COOH

CH$_3$—CH = CH—COOH → CH$_3$—C̆—CH$_2$ COOH → CH$_3$—CO—CH$_2$—COOH
Crotonic acid, normal form Activated forms Final forms

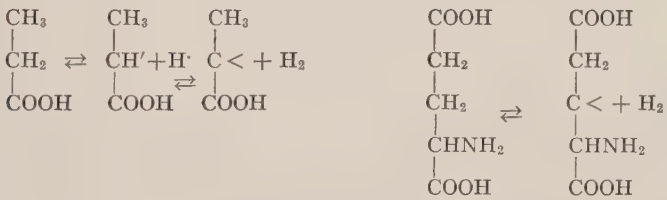
Quastel offers the following picture of the activation of the saturated carbon bond, showing the equilibria represented in Wieland's theory:



The activation of succinic acid follows this course:



In the cases of propionic acid and of glutamic acid activation would follow these lines:



Quastel, in drawing these conclusions, states that he has been acting under Thomson's guidance. Thomson was the discoverer of the electron.

Mention should be made of the valuable studies of Mansfield Clark,[1] whose views are not in entire accord with those above outlined.

It may be added that, if by hydrolysis fumaric acid is converted into malic acid, the cleavage of CO_2 will leave lactic acid, a substance which is completely convertible into glucose by the diabetic dog. Since three of the four carbon atoms in succinic acid are convertible into glucose by the diabetic dog (see p. 244), it seems likely that the pathway indicated in the formula is correct. If the activated form of propionic acid is hydrolyzed, it also becomes lactic acid and is completely convertible into sugar in diabetes. The activated form

[1] Clark, M.: Proc. Roy. Soc. (London), 1927, B, **101**, 57.

of glutamic acid by hydrolysis becomes β-hydroxyglutamic acid (see p. 243). If this loses its acetyl group, serin remains. Serin is completely convertible into glucose in diabetes (see p. 238) and three of five carbon atoms in glutamic acid and in β-hydroxyglutamic acid are so convertible (see p. 243).

That iron does not act in accord with Warburg's theory has already been discussed when describing the oxidation of cystein. Harrison[1] has reached a similar conclusion with regard to the glutathion oxidation-reduction system and gives his views in a paper describing the catalytic action of traces of iron on the anaerobic oxidation of sulphydryl compounds. He finds that there is no essential difference in the anaerobic and aerobic systems, both of which are accelerated in their action by the presence of iron. He regards it as probable that the reaction proceeds by an alternate oxidation and reduction of an iron sulphydryl complex rather than through the mediation of free inorganic iron. Since hydrocyanic acid inhibits not only aerobic but also anaerobic oxidation of sulphydryl compounds, the inhibition by cyanide in an oxidizing system does not justify the assumption that oxygen activation must be a necessary part of that system.

Miss Thurlow[2] has found that hypoxanthin in the presence of the specific dehydrase (xanthin "oxidase") is oxidized in the presence of molecular oxygen with the production of peroxide of hydrogen. Thus molecular oxygen seems to act as a direct acceptor of hydrogen in this scheme. It constitutes an exact illustration of Wieland's theory. Dixon and Thurlow[3] find that this oxidation is not inhibited by adding cyanide nor pyrophosphate. Addition of iron produces no acceleration, hence activation by Fe does not occur in this system. This contradicts Warburg's statement that *only* through the reaction of molecular oxygen with iron is it possible to oxidize organic substances in the cell.

Meyerhof[4] has described what he called a co-enzyme to respiration. Working with aceton yeast and frog's muscle, he found that the velocity of oxidation could be very considerably reduced by exhaustive washing and could afterward be restored by the addition of an extract of yeast or of animal tissues made with boiling water.

[1] Harrison, D. C.: Biochem. J., 1927, **21,** 335.
[2] Thurlow, S.: *Ibid.*, 1925, **19,** 175.
[3] Dixon, M., and Thurlow, S.: *Ibid.*, p. 672.
[4] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1918, **170,** 367; *Ibid.*, 1919, **175,** 20.

However, Holden[1] has shown that if these extracts be previously aerated with oxygen for several hours they lose their power of being "respiration substances." They probably contain a lot of oxidizable substances themselves, which he believes explains their action in Meyerhof's experiments.

An important discovery of a respiratory pigment, *cytochrome*, common to animals, yeast, and the higher plants, was made by Keilin.[2] Cytochrome contains a hemochromogen nucleus. The highest concentration of this pigment is found in the thoracic wing muscles of flying insects, the striated muscles of mammals and birds, and in baker's yeast. It readily undergoes oxidation and reduction. It is too early to forecast the importance of cytochrome. However, Barbara Holmes[3] finds that rat carcinoma and sarcoma contain abnormally small quantities both of reduced glutathion and of cytochrome. In this she finds support of the opinion of Warburg,[4] that cancer cells resemble anaerobic rather than aerobic organisms.

Voegtlin and Thompson[5] report, regarding the glutathion content of tumor animals, that as the tumors grow larger the glutathion content of the rest of the body declines, and they suggest that the cachexia of cancer may be due to this cause.

If one returns to the fundamental proposition that oxidation depends on the mechanism of the cell and not on the quantity of oxygen, a striking example is found in the experiments of Lund[6] upon *Paramecium caudatum*. Lund found that the rate of intracellular oxidation was the same when the concentration of oxygen varied 55-fold, from 0.04 c.c. to 2.2 c.c. per 137 c.c. of liquid. Pertinent also is the statement that potassium cyanide in doses which do not produce cytolysis does not affect the oxidation process.

As the discussion of the fate of the broken fragments of the various food-stuffs proceeds, the method of their oxidation will assume new importance.

[1] Holden, H. F.: Biochem. J., 1923, **17**, 361.
[2] Keilin, D.: Proc. Roy. Soc. (London), 1925, B, **98**, 312.
[3] Holmes, B. E.: Biochem. J., 1926, **20**, 812.
[4] Warburg, O.: J. Cancer Res., 1925, **9**, 148.
[5] Voegtlin, C., and Thompson, J. W.: J. Biol. Chem., 1926, **70**, 801.
[6] Lund, E. J.: Am. J. Physiol., 1917–18, **45**, 351, 365.

CHAPTER IX

THE INFLUENCE OF PROTEIN FOOD

PART I—NITROGEN EQUILIBRIUM

This generalizing farther than the observed facts warrant, this tendency to assume that our feeble, finite minds have at any time attained to a complete understanding even of the basis of the physical universe, this sort of blunder has been made over and over again in all periods of the world's history and in all domains of thought.—R. A. Millikan.

Protein contains the magic of life, ever newly created and then dying, a process continuous since the advent of life upon the earth. In the lower forms of life it requires only a few minutes for dead protein to awake as living matter, endowed with all the inherited biological and chemical attributes of the given cell.—Rubner, 1920.

It has been thought that protein is a food which is in itself sufficient for all the requirements of the body. Pflüger[1] was able to keep a very thin dog in good condition and doing active exercise during a period of seven months, the sole diet being meat cut as free from fat as possible. Pflüger says that the fat and glycogen content of the meat ingested could not have yielded sufficient energy to provide for the action of the heart alone. It must be remembered, however, that meat is not pure protein, but is mixed with fat, salts and water. The simplest diet capable of maintaining the body in condition is, therefore, a mixture of materials or food-stuffs. Such a mixture of food-stuffs is called a food. A food-stuff is a material capable of being added to the body's substance, or one which when absorbed into the blood-stream will prevent or reduce the wasting of a necessary constituent of the organism.

The food-stuffs are:

Proteins (including albuminoids).
Carbohydrates.
Fats.
Salts.
Water.

A food is a palatable mixture of food-stuffs which is capable of maintaining the body in an equilibrium of substance, or capable of

[1] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1891, **50**, 98.

bringing it to a desired condition of substance. The ideal food is a palatable mixture of food-stuffs arranged together in such proportion as to burden the organism with a minimum of labor. These definitions are Voit's.[1]

When protein alone is ingested by a normal adult it is very readily oxidized, and is only with the greatest difficulty deposited so as to form new tissue in the organism.

In the early experiments of Bischoff and Voit the fact is recorded that a dog weighing 35 kilograms may excrete 12 grams of urea in twenty-four hours, and the same dog after receiving 2500 grams of meat may excrete 184 grams, fifteen times as much (see p. 79).

Voit[2] has shown that if that quantity of meat be administered which corresponds to what is oxidized in starvation, nitrogen equilibrium will not be established, but some of the body's flesh will also be metabolized. This latter quantity grows steadily less if the amount of meat ingested be gradually increased until finally the point of *nitrogen equilibrium* is reached, at which the amount of meat ingested is equal to that destroyed in the body. To illustrate this Voit gives the following table, the results of work done on a dog:

Grams Meat Administered	Grams Flesh Destroyed	Change in the Body
0	233	−233
0	190	−190
300	379	− 79
600	665	− 65
900	941	− 41
1200	1180	+ 20
1500	1446	+ 54

Nitrogen equilibrium was not reached until 1200 grams of meat were given, or about five times the amount of the fasting protein metabolism.

The above experiments were made in 1858. It is no longer customary to calculate the protein metabolism in terms of flesh destroyed, but in terms of nitrogen. The old-fashioned term "flesh" meant meat with a nitrogen content of 3.4 per cent. It served to illuminate the significance of metabolism at a time when few were instructed in this field of work.

E. Voit and Korkunoff[3] have published a research of similar character. They fed a dog with meat which had been treated with lukewarm water to remove the extractives, and which was then

[1] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Pt. 1, pp. 330, 344.
[2] Voit, C.: *Ibid.*, 1881, p. 106.
[3] Voit, E., and Korkunoff, A.: Z. f. Biol., 1895, **32**, 58.

squeezed in a press. This process removes most of the nitrogen-containing substances other than protein. A dog will readily eat this washed meat or "protein." The idea was to determine the minimum quantity of protein which it was possible to ingest and still maintain nitrogen equilibrium. The different quantities of meat tabulated below were given continuously for two or three days at a time. Only the results of the last day of each of these periods are quoted:

Food	N in Food	N in Excreta	Difference
Starvation	0	3.996	−3.996
100 gm. meat	4.10	5.558	−1.458
140 " "	5.74	6.495	−0.755
165 " "	6.77	7.217	−0.447
185 " "	7.59	7.804	−0.214
200 " "	8.20	8.726	−0.526
230 " "	10.24	10.579	−0.339
360 " "	11.99	12.052	−0.062
410 " "	15.58	14.314	+1.266
360 " "	13.68	13.622	+0.058
Starvation, third day	.....	4.026	−4.026

The figures show that nitrogen equilibrium was reached only after supplying three and a half times the amount of protein metabolized in starvation. The authors calculate that at this time of nitrogen equilibrium the dog was still losing 28 grams of body fat, and that not much more than 50 per cent. of the total energy liberated in the organism was furnished by the protein metabolism of the time. *One may thus have nitrogen equilibrium without having carbon equilibrium.*

Systems of diet for fat people are based on this knowledge. A loss of protein is highly undesirable, while a gradual loss of adipose tissue may be a great relief to the obese.

Bornstein[1] finds that during a period of thirteen days he can add 8.3 grams of protein to his body and oxidize 90 grams of body fat daily when ingesting a mixed diet containing 1600 calories with 118 grams of protein. Such a diet contains a fuel value less than the requirement of his organism (p. 365).

This cannot be accomplished without carbohydrate in the diet, for Thomas[2] finds that when a man is given protein alone, administered in fractional portions every two hours even to the extent of double the quantity of protein destroyed in fasting, nitrogen equilibrium cannot be obtained. This experiment is given below; 500 grams

[1] Bornstein, K.: Berliner klin. Wchnschr., 1904, **41**, 1192, 1226.
[2] Thomas, K.: Arch. f. Physiol., 1910, Suppl., p. 249.

of meat contained 18.4 grams of nitrogen, corresponding to about 115 grams of protein:

Day	6	7	8	9	10	11	12	13	14	15
N in food	.....	.....	8.63	8.63	8.63	15.54	17.27	18.39	18.40	18.39
N in urine	7.64	9.78	12.90	13.46	14.42	16.81	18.92	20.85	21.50	21.52
± N to body	−8.16	−10.00	−4.79	−4.79	−6.31	−1.79	−2.17	−2.97	−3.62	−3.64

If the quantity of meat ingested be steadily increased after nitrogenous equilibrium has been reached, the protein metabolism will gradually increase, nitrogenous equilibrium will be established at higher and higher levels, and there will be a corresponding diminution in the amount of fat burned. This was shown in 1862 in the following experiment of Voit,[1] who gave different quantities of meat to a large dog weighing 30 kilograms.

INFLUENCE OF INGESTING INCREASING QUANTITIES OF MEAT
(Weights are in grams)

Meat Ingested	Flesh Destroyed	Gain or Loss of Body Flesh	Gain or Loss of Body Fat	O_2	CO_2	R. Q.
0	165	−165	−95	330	327	.72
500	599	− 99	−47	341	356	.76
1000	1079	− 79	−19	453	463	.74
1500	1500	0	+ 4	487	547	.81
1800	1757	+ 43	+ 1	...	656	
2000	2044	− 44	+58	517	604	.84
2500	2512	− 12	+57	...	783	

Nitrogen equilibrium existed after the ingestion of 1500 grams of meat and there was also no loss of body fat (carbon equilibrium). When 2000 grams and even 2500 grams of meat were supplied it was all destroyed, as was indicated by the amount of nitrogen in the urine, but a certain quantity of carbon belonging to the ingested protein was not eliminated in the respiration, but was retained in the body. This carbon Pettenkofer and Voit believed to have been laid up in the body in the form of fat. This subject will be elaborated in Chapter XI.

The respiratory quotient in the foregoing series gradually rises, as would be expected from the increasing prominence of the protein in the metabolism (p. 64). Meat alone will therefore support a dog. Rubner[2] says that a man cannot live on meat alone, not

[1] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, 6, Pt. 1, p. 117.
[2] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, 1, 42.

because the intestinal canal cannot digest it, but because of the physical limitations of the apparatus of mastication. A dog weighing 10 kilograms may ingest 1000 grams of chopped meat in forty-five seconds, while a man requires between five and ten minutes rapidly to cut and partake of 200 grams of good sirloin steak.

A subject of interest in considering the value of protein in metabolism is that of the value of gelatin. Gelatin is an artificial derivative of collagen, an albuminoid largely found in the skeletal structure of animals. Gelatin contains very nearly the same quantity of nitrogen as protein; it breaks up on chemical treatment into the same amino-acids, except that it does not yield tyrosin, cystin, and tryptophan. In the diabetic, gelatin yields the same amount of sugar as does protein.[1] To what extent gelatin may take the place of protein in the body's metabolism has long been the subject of inquiry.

It was shown first by Bischoff and Voit[2] that no matter how much gelatin was ingested, it was always completely burned, and some of the body's protein in addition. Therefore gelatin never builds up new tissue, although it may somewhat diminish tissue waste. Gelatin may be formed from protein in the body, but it cannot be reconverted into protein nor act like protein in metabolism. Kirchmann,[3] working in the laboratory of Erwin Voit, has shown to what extent gelatin spares protein in metabolism. If one takes the amount of protein metabolism in starvation as one, then the ingestion of about the same quantity of gelatin reduces the body's protein waste 23 per cent., and if eight times this amount of gelatin be given, the tissue waste may be reduced 35 per cent. In other words, the ingestion of 7.5 per cent. of the total heat requirement of the organism in the form of gelatin spares 23 per cent. of the body's protein, while the ingestion of 60 per cent. of the requirement will cause a decrease of only 35 per cent. in protein waste. Krummacher[4] showed that the ingestion of the full heat requirement of the animal in the form of gelatin reduced the fasting protein metabolism by only 37.5 per cent. It is evident that no matter how much gelatin be given, tissue protein continues to be destroyed, and it is also evident that a small quantity of gelatin has almost as great an effect as a large quantity.

[1] Reilly, F. H., Nolan, F. W., and Lusk, G.: Am. J. Physiol., 1898, **1**, 395.
[2] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Pt. 1, p. 396.
[3] Kirchmann, J.: Z. f. Biol., 1900, **40**, 54.
[4] Krummacher, O.: *Ibid.*, 1901, **42**, 242.

An extremely interesting experiment of Kauffmann[1] shows that when the lacking tyrosin, cystin, and tryptophan are mixed with gelatin in the proportions in which they occur in true protein, and are given to a dog or to a man, nitrogen equilibrium may be established. Abderhalden[2] confirms this in similar experiments.

It is evident, therefore, that the value of the various proteins in nutrition may depend upon their constituent amino-acids, and this will be considered on another occasion (see p. 511).

It appears that protein bodies must be broken up into amino-acids before absorption in the intestine (p. 84). If this be true, then ingestion of the cleavage products of protein should maintain nitrogen equilibrium in the same way as the ingestion of meat. The first experiments in this direction were done by Loewi,[3] who gave a dog pancreas which had been self-digested until all the protein had been converted into amino-acids, as was indicated by the almost complete disappearance of the biuret reaction. Fat and carbohydrates were given with the digest, and nitrogen equilibrium was obtained and even nitrogen retention accomplished. Thus, in one experiment covering a period of eleven days, proteolytic digestive products containing an average of 6.08 grams of nitrogen were given daily, of which only 5.19 grams were eliminated in the excreta, while the balance, or 0.89 gram of nitrogen, was retained in the body of the animal. This amounted to 9.79 grams of nitrogen in eleven days. Accompanying this nitrogen retention was one of 0.649 gram of phosphoric acid (P_2O_5), an amount larger than was necessary for the upbuilding of new tissue from the nitrogen compounds retained. Loewi concluded that he had demonstrated the synthesis of new protein within the organism.

Henderson and Dean[4] confirmed Loewi by finding that they could obtain nitrogen equilibrium by feeding a dog with the cleavage products of meat produced by treatment with sulphuric acid.

Abderhalden and Rona[5] found that mice live on casein split with pancreatin as long as they do on casein alone; whereas they die much earlier if the casein has been submitted to peptic and then pancreatic digestion, or if it has been broken up by acid hydrolysis. Henriques

[1] Kauffmann, M.: Pflüger's Arch. gesam. Physiol., 1905, **109**, 440.
[2] Abderhalden, E.: Z. physiol. Chem., 1912, **77**, 22.
[3] Loewi, O.: Arch. exper. Path. u. Pharm., 1902, **48**, 303.
[4] Henderson, Y., and Dean, A. L.: Am. J. Physiol., 1903, **9**, 386.
[5] Abderhalden, E., and Rona, P.: Z. physiol. Chem., 1904, **42**, 528.

and Hansen[1] also find that casein broken up by acid will not maintain nitrogen equilibrium in rats, but that if the pancreas of the ox and a small piece of the intestine of the dog (to furnish erepsin) be digested for two months at 40°, and the resulting material given to rats, nitrogen equilibrium will be maintained. The authors further find that the mono-amino-acid fraction (the filtrate after precipitation with phosphowolframic acid) and also the alcoholic extract of the last-named digest maintain rats in nitrogen equilibrium. The residue left after alcoholic extraction will not do so.

Abderhalden and Rona[2] have accomplished a most interesting experiment upon a dog. The animal was given daily a constant quantity of non-nitrogenous foods which were: fat, 25 grams; starch, 50 grams; cane-sugar, 10 grams; glucose, 5 grams. The dog was brought into nitrogen equilibrium by giving him meat containing 2 grams of nitrogen. Then for this were substituted the amino cleavage products of casein, produced by pancreatic digestion and also containing 2 grams of nitrogen. During sixteen days on this diet there was an average daily gain of 0.12 gram of nitrogen by the dog. Then casein hydrolized by acid and containing 2 grams of nitrogen was administered for ten days, during which time the dog lost 0.48 gram of nitrogen daily. Amino products prepared after this fashion will, therefore, not preserve nitrogen equilibrium. Lastly, the diet was continued without any nitrogenous food. The daily waste of body nitrogen was then 0.53 gram. The loss was the same as when the casein hydrolized by acid was ingested, indicating that this particular array of cleavage products had no protecting power over the body protein.

Henriques[3] has hydrolized protein by digesting it with trypsin and erepsin and then treating with 20 per cent. sulphuric acid on the water-bath. The resulting material consists entirely of amino-acids with no admixture of polypeptids, and if it still gives a pronounced tryptophan reaction it will support the organism in nitrogen equilibrium. *In the absence of the single amino-acid tryptophan, nitrogen equilibrium cannot be attained.*

That the mixture of amino-acids must be complete is shown by the fact that, if asparagin, 20 gm., leucin, 3 gm., tyrosin, 3 gm., tryptophan, 2 gm., glutamic acid, 3 gm., and alanin, 6.5 gm., (5.87

[1] Henriques, V., and Hansen, C.: Z. physiol. Chem., 1904–05, **43**, 417.
[2] Abderhalden, E., and Rona, P.: *Ibid.*, 1905, **44**, 198.
[3] Henriques, V.: *Ibid.*, 1907–08, **54**, 406.

gm. N in all), be added to a standard nitrogen-free diet and given to a dog weighing 20 kg., nitrogen equilibrium cannot be obtained. This was shown by Seuffert and Marks,[1] who found that, whereas the body lost 3 gm. nitrogen when the nitrogen-free diet was given, it lost 1.7 gm. nitrogen when the above-described amino-acid mixture was added. The mixture therefore spared body protein, as do indeed individual amino-acids,[2] but did not replace completely the broken parts. To do this the addition of cystin and lysin occurs to one as necessary.

To complete the story, the work of Abderhalden[3] must be recited. Nitrogen equilibrium and even nitrogen retention were established in a dog when the diet contained instead of protein the following mixture of pure amino-acids: Glycin 5 grams, d-alanin 10 grams, l-serin 3 grams, l-cystin 2 grams, d-valin 5 grams, l-leucin 10 grams, d-isoleucin 5 grams, l-aspartic acid 5 grams, d-glutamic acid 15 grams, l-phenyl-alanin 5 grams, l-tyrosin 5 grams, l-lysin 5 grams, d-arginin 5 grams, l-prolin 10 grams, l-histidin 5 grams, and l-tryptophan 5 grams. This mixture weighed 100 grams and contained 13.87 grams of nitrogen. It is not unlike ox muscle in relative composition (see p. 83).

It is therefore proved that amino bodies resulting from certain proteolytic cleavages may be the equivalent in metabolism of ingested protein itself.

In practical dietetics these substances can have little value, as they tend to produce diarrhea, as do also albumoses and peptones when given in any considerable quantity.[4] As illustrating this Cronheim[5] finds that though "Somatose" is more digestible than meat, still over 30 grams are undesirable in the daily diet of a man.

It is certain that if there be a new construction of protein in the body from the amino-acids formed in digestion such new proteins are characteristic of the organism, and do not possess the properties of the proteins originally ingested. To illustrate this Abderhalden and Samuely[6] gave to a horse 1500 grams of gliadin, a vegetable protein which contains 36.5 per cent. of glutamic acid. They wondered if

[1] Seuffert, R. W., and Marks, E.: Z. f. Biol., 1925, **82,** 244.
[2] Levene, P. A., and Kober, P. A.: Am. J. Physiol., 1908–09, **23,** 324; Abderhalden, E., and Markwalder, J.: Z. physiol. Chem., 1911, **72,** 63.
[3] Abderhalden, E.: *Ibid.*, 1912, **77,** 22.
[4] Voit, F.: Münchener med. Wchnschr., 1899, **46,** 172.
[5] Cronheim, W.: Pflüger's Arch. gesam. Physiol., 1905, **106,** 17.
[6] Abderhalden, E., and Samuely, F.: Z. physiol. Chem., 1905, **46,** 193.

the ingestion of such a protein would in any way modify the composition of the proteins of the blood-serum, of serum globulin which under ordinary circumstances contains 8.5 per cent., and of serum albumin which contains 7.7 per cent. of glutamic acid. Their results were as follows:

INFLUENCE OF GLIADIN INGESTION ON THE PERCENTAGE OF GLUTAMIC ACID IN THE SERUM PROTEINS OF THE HORSE

Experiment	Normal Day	After Fasting 7 or 8 Days	After Ingesting 1500 G. Gliadin Day 1	Day 2
I.	8.85	8.20	7.88	8.25
II.	9.52	8.52	8.00	

It is evident that gliadin, which contains so large a proportion of glutamic acid, is without influence on the composition of the blood-serum. Abderhalden conceived that such proportions of the amino-acids within the gliadin complex as are available for the formation of new serum albumin and serum globulin were used for the generation of these proteins. Evidence that amino-acids enter the blood-stream directly from the intestinal tract has already been submitted. Furthermore, Henriques and Andersen[1] have administered continuous intravenous injections of meat hydrolized with trypsin and erepsin to goats which had survived the operation of extirpating the intestines, and have noted nitrogen retention. From this they conclude that the intestine is not necessary for protein regeneration.

It has already been stated (p. 80) that if the serum of a dog be injected into the blood-vessels of another dog the nitrogen of it will be eliminated in the urine. This is also true of proteins foreign to the organism, and these likewise act in a toxic manner to destroy body protein. Thus Mendel and Rockwood[2] have shown that if edestin, a pure crystalline protein prepared from hemp seed, be injected intravenously into a fasting dog, there is for two days a metabolism of protein which is much greater than that of former days plus that of the edestin administered. The same truth holds when casein is injected. Similar injection of horses' serum into dogs appears to have no toxic action (Rona and Michaelis[3]). This work is of interest in connection with the subject of *anaphylaxis*, called also the Theobald Smith phenomenon, which has been especially investigated by

[1] Henriques, V., and Andersen, A. C.: Z. physiol. Chem., 1914, **92**, 194.
[2] Mendel, L. B., and Rockwood, E. W.: Am. J. Physiol., 1904–05, **12**, 350.
[3] Rona, P., and Michaelis, L.: Pflüger's Arch. gesam. Physiol., 1908, **121**, 163; 1908, **123**, 406.

Rosenau and Anderson. Injections of a protein foreign to the organism render the body sensitive to a second injection of the same protein. Large or small amounts of foreign protein may be injected in the first instance without intoxication, but if the animal be once "sensitized" a small amount of the same protein will terminate the animal's existence. It has recently been stated by Wells[1] that the injection of so minimal an amount as $\frac{1}{1,000,000}$ gram of pure crystalline egg-albumin will "sensitize" a guinea-pig so that a subsequent injection into the blood of $\frac{1}{10}$ milligram of the same substance is lethal, although such a dose given in the first instance would not have injured the animal. It is evident, therefore, that the alimentary canal does not usually allow the passage of proteins without changing them. This also explains the complete immunity of the organism to snake venom which has been swallowed.

Dogs which are fed with a constant diet, show a positive nitrogen balance following the removal of blood,[2] as is the case also in women after the menstrual period (see p. 526) and Abderhalden and Roske find that intravenous injection of 110 c.c. of dog's blood into a dog maintained on a constant diet does not result in as great an extra output of nitrogen as is the case when 60 c.c. of human blood are injected.

The effect of copious drinking of water upon protein metabolism has been made the subject of various studies. A small increase in nitrogen elimination has usually been noted. This was first established by Voit, who explained it as due to an increased circulation which influenced the flow of the intracellular fluids. Heilner[3] has shown that giving 2000 c.c. of water to a fasting dog on two successive days raises his urinary nitrogen from 3.15 grams to 4.09 and 3.58 grams on the two days of water ingestion, and then the nitrogen excretion falls to 2.22 and 2.62 on the following days. In this experiment the carbon dioxid excretion was very slightly increased and the temperature of the dog was not affected. The quantity of urine rose from 90 to 2050 c.c.

Straub[4] found that an extra ingestion of 2000 c.c. of water in a man who was in nitrogen equilibrium on a diet containing 20.56 grams of nitrogen had no effect on protein metabolism; whereas

[1] Wells, H. G.: Proc. Soc. Exper. Biol. and Med., 1908, **6**, 1.
[2] Abderhalden, E., and Roske, G.: Pflüger's Arch. gesam. Physiol., 1926, **214**, 207.
[3] Heilner, E.: Z. f. Biol., 1906, **47**, 541.
[4] Straub, W.: *Ibid.*, 1899, **37**, 527.

Hawk,[1] who gave less protein nitrogen but more water, found that the ingestion of 4500 c.c. of water caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second day, with a fall to 10.91 grams on the succeeding day when no water was given. Hawk interprets the action of copious water drinking as twofold: *first*, to cause a removal of any accumulation of nitrogenous decomposition products from the organism, as was indicated by the greater increase of 12.8 per cent. in the nitrogen elimination of the first day; and, *second*, to cause a true increase in protein metabolism, as was indicated by the smaller increase of 6.8 per cent. on the second day of water ingestion.

Abderhalden and Bloch[2] have given a fixed diet to a person suffering from alcaptonuria (see p. 213) and on one of the days of the experiment have caused him to ingest 5 liters of water. The results of their analyses gave the following figures in grams:

	N Balance	N in Urine	Homogentisic Acid
Normal food	+1.36	18.2	10.52
" " + 5 l. water	**−2.19**	**21.75**	**10.18**
" "	+1.47	18.09	10.27

Abderhalden believes that the constancy of the output of homogentisic acid indicates a constancy of protein metabolism throughout, whereas the rise in total nitrogen elimination in the urine represents a washing out of the nitrogenous end-products as a result of the large ingestion of water.

THE CURVE OF NITROGEN ELIMINATION

One of the striking characteristics of starvation metabolism was shown to be its extreme regularity from hour to hour and from day to day. What, then, is the hour-to-hour metabolism after meat ingestion?

The classical experiments of Voit[3] and of Feder[4] have been more fully worked over by Gruber. Gruber[5] fed a dog with 500, 1000, and 1500 grams of meat on different days. He collected the urine every two hours after the meal and determined the nitrogen output. The

[1] Hawk, P. B.: University of Pennsylvania Med. Bull., March, 1905.
[2] Abderhalden, E., and Bloch, B.: Z. physiol. Chem., 1907, **53**, 464.
[3] Voit, C.: "Physiologisch-chemische Untersuchungen," Augsburg, 1857, p. 42.
[4] Feder, L.: Z. f. Biol., 1881, **17**, 541.
[5] Gruber, M.: *Ibid.*, 1901, **42**, 421.

curves of nitrogen elimination under these circumstances are as follows:

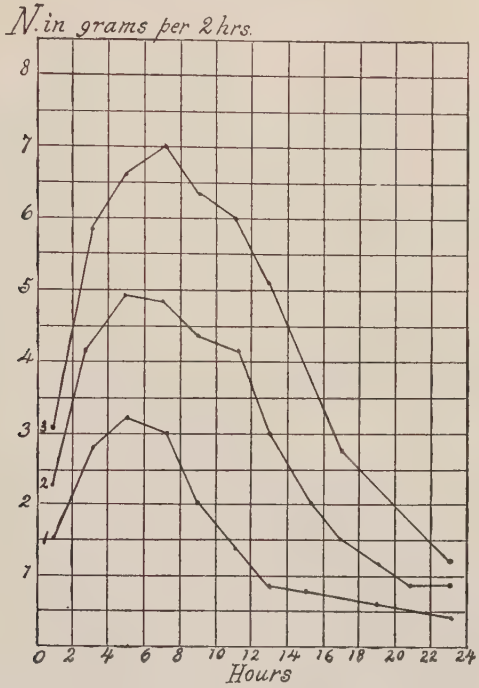


Fig. 13.—1, After 500 g. meat + 50 g. fat + 350 c.c. water; 2, after 1000 g. meat + 200 c.c. water; 3, after 1500 g. meat + 500 c.c. water. On each of these days the animal was in nitrogen equilibrium.

It is evident that there is an early elimination of protein nitrogen which here reaches a maximum between five and seven hours after feeding, and that the hour of the maximum excretion is delayed by increasing the quantity of meat ingested.

Feder found that fat when given with protein delayed its absorption. Firgau, Hartmann and E. Voit[1] find that when much carbohydrate is given with meat the curve of urinary nitrogen elimination is the same as that given by Feder in 1881 for meat alone.

It is apparent, therefore, that the protein metabolism as illustrated by the curve of nitrogen elimination is quite different from its even metabolism in starvation.

Kugler,[2] in the Munich laboratory of E. Voit, has given 300 gm. of meat each to four small dogs of similar weights and killed them 2,

[1] Firgau, H., Hartmann, K., and Voit, E.: Z. f. Biol., 1927, **85**, 557.
[2] Kugler, K.: *Ibid.*, 1918–19, **69**, 437.

4, 8, and 12 hours after food ingestion. He analyzed the content of stomach and small intestine for nitrogen at these different intervals and found the following data:

No. of the dog	2	3	5	6
Weight, kg	6.9	7.1	7.4	8.3
Hours between food and death	2	4	8	12
N in diet, gm	15.8	15.7	15.6	17.8
N in stomach, gm	13.3	10.9	5.0	2.0
N in small intestine, gm	0.89	1.07	1.03	0.91
N absorbed, per cent	8.7	23.3	59.1	81
N absorbed per hr., gm. (calculated by G. L.)	0.69	1.14	1.39	0.97

Apparently a very constant source of supply of protein was present in the intestines, 80 per cent. of which, the author states, was in the form of polypeptids or amino-acids. The rate of absorption compares quite closely with the curve of urinary nitrogen elimination.

Abderhalden[1] has isolated from the intestinal tract not only simple amino-acids in quantity but also dipeptids such as glycyl-l-phenylalanin, and l-leucyl-l-tryptophan; and from a trypsin digestion of gliadin he has obtained l-leucyl-d-glutamic acid.

Haas[2] in experiments on man finds that the curve of nitrogen elimination after a breakfast consisting of milk, bread, butter, and cheese always shows two maxima, the first in the second hour and the second in the fifth. The first rise in the curve is due to the removal of nitrogenous end-products already in the system and is caused by the early absorption of liquids taken with the food. The second rise corresponds to the absorption of food protein. Haas believes this to be the true explanation, because if diuresis be first induced by drinking tea, with a consequent washing out of urea from the body, then partaking of breakfast no longer causes so high a primary rise of nitrogen elimination, nor is the total elimination so great as in the experiments without preliminary diuresis. The experiment shows that for short periods the nitrogen excretion is not a true index of urea production. Severe muscular work had no influence upon the character of the curve described except when the quantity of urine produced is diminished, in which case the urea elimination is also reduced.

[1] Abderhalden, E.: Z. physiol. Chem., 1912, **78**, 382; 1912, **81**, 315; 1921, **114**, 290; 1926, **154**, 18.

[2] Haas, E.: Biochem. Z., 1908, **12**, 203.

Confirming Albarran,[1] Barringer and Barringer[2] note that the volumes and the nitrogen content of the urine from the two kidneys are almost identical.

Urea in the organism undergoes no chemical change; there is no reversible reaction in the sense of ammonia formation, except for the neutralization of acids in the kidney (see p. 263).[3] When urea is retained in the body it is found widely distributed in all the tissues excepting fatty tissue; if it be administered intravenously to a dog diffusion to all parts of the body is complete in a few minutes.[4] A concentration of 1.2 per cent. may sometimes be reached in the dog, though one of over 1 per cent. is usually fatal, the animal dying in convulsions.

The amount of urea excretion is found to be closely parallel to the urea concentration of the blood. This relation was formulated in Ambard's laws of urea elimination.[5]

(1) When the concentration of urea in the urine is constant the quantity of urea excreted in the urine varies proportionately to the square of the concentration of urea in the blood.

(2) When the concentration of urea in the blood remains constant the quantity excreted in the urine varies inversely as the square root of the concentration in the urine.

From these laws Ambard's coefficient or constant for the urea elimination through the kidney of human subjects was evolved. Arbitrary standards of normal weight, such as 70 kilograms, and of urea excreted in twenty-four hours, such as 25 grams, were adopted in the formula, which is as follows:

$$\frac{Ur}{\sqrt{D} \times \frac{70}{Wt} \times \sqrt{\frac{C}{25}}} = K \text{ or Constant of Ambard.}$$

Ur = Urea per liter of blood in grams.
D = Urea in urine in twenty-four hours in grams.
Wt = Weight of patient in kilograms.
C = Concentration, or grams urea per liter of urine.

Ambard found the constant in normal individuals varied between 0.06 and 0.07. McLean,[6] who has used more accurate methods for

[1] Albarran, J.: "Exploration des fonctions rénales," Paris, 1905, p. 329.
[2] Barringer, T. B., Jr., and Barringer, B. S.: Am. J. Physiol., 1910–11, **27**, 119.
[3] Janney, N.: Z. physiol. Chem., 1911–12, **76**, 99.
[4] Marshall, E. K., Jr., and Davis, D. M.: J. Biol. Chem., 1914, **18**, 53. Confirmed by Leiter, L.: Arch. Int. Med., 1921, **28**, 331.
[5] Ambard, L.: Compt. rend. soc. biol., 1910, **69**, 506.
[6] McLean, F. C.: J. Exper. Med., 1915, **22**, 212.

measuring urea, finds the constant to be nearer 0.08, with wider variations than French observers found. This coefficient is being applied to determine kidney efficiency in renal disease. When the coefficient is found to be much increased, then urea is being retained by the organism on account of renal insufficiency.

Citing from McLean and Selling,[1] the following results may be given:

Person	Time	Urea N			Ambard's Coefficient
		In Blood	In Urine		
			In 24 Hours	Per Liter	
F. C. M.	Forty-five minutes after 10 gm. urea	Mg. 24	Grams 24.6	Grams 16.4	0.068
F. C. M.	Three days low protein diet	14	6.9	9.7	0.085
H. K. A.	After heavy dinner	22	11.4	11.6	0.088
B.	Nephritic	29	9.6	7.6	0.150

In some interesting work Pepper and Austin[2] find that after giving 900 grams of meat to a dog the non-protein nitrogen in the blood rises rapidly from 20 to 60 mg. per 100 c.c., and the urinary nitrogen rises from 0.15 gram to 1.1 grams per hour.

It is evident from this analysis that the curve of nitrogen elimination is not an exact indicator of the time relations of the breaking up of amino-acids in the body, for a part of the urea formed accumulates in the blood and is not at first eliminated in the urine, and too low a protein metabolism may thus be computed in error. Later, with a diminished absorption of amino-acids and diminished production of urea, the excess which is not attributable to the metabolism of the moment is eliminated from the blood, and the urinary nitrogen of these hours will give too high figures if used to compute the protein metabolism of short periods (see p. 207).

Walker and Rowe[3] in a recent review conclude that the first law of Ambard is only a rough approximation, and the second is completely invalid. This confirms the opinions of Austin, Stillman and Van Slyke.[4]

[1] McLean, F. C., and Selling, L.: J. Biol. Chem., 1914, **19**, 31.
[2] Pepper, O. H. P., and Austin, J. H.: *Ibid.*, 1915, **22**, 81.
[3] Walker, B. S., and Rowe, A. W.: Am. J. Physiol.; 1927, **81**, 738.
[4] Austin, J. H., Stillman, E., and Van Slyke, D. D.: J. Biol. Chem., 1921, **46**, 91.

Addis and Drury[1] have given to men 1000 c.c. of water containing variable quantities of urea and have observed that under these conditions the rate of urea excretion becomes directly proportional to the concentration of urea in the blood. Over a wide range the

$$\frac{\text{urea in urine of 1 hour}}{\text{urea in 100 c.c. blood}}$$

is a constant within narrow limits, and changes in the volume of urine secreted have no demonstrable effect on the rate of urea excretion. One of their tables is given below:

EFFECT OF THE CHANGES IN BLOOD UREA CONCENTRATION ON THE RATE OF UREA EXCRETION

Subject A			Subject B		
Blood Urea	Urine Urea	Urine Urea / Blood Urea	Blood Urea	Urine Urea	Urine Urea / Blood Urea
Mg. per 100 c.c.	Mg. per hr.		Mg. per 100 c.c.	Mg. per hr.	
17.7	750	42.4	20.2	1180	58.4
49.5	2070	41.8	49.7	2910	58.6
93.5	4220	45.1	97.5	5620	57.7
			108.0	6100	56.5

Kast and Wardell[2] conclude that for diagnostic purposes for the estimation of a properly functioning kidney 20 mg. urea nitrogen in the blood may be taken as the normal upper limit.

It may here be noted that the elimination of sodium chlorid follows Ambard's laws in the behavior of that quantity which is in excess of 5.62 grams of NaCl per liter of blood-plasma[3] (see p. 718) which is the threshold value of elimination by the kidney.

THE CURVE OF SULPHUR ELIMINATION

It was shown by Rubner,[4] who gave washed meat containing 24.72 grams of nitrogen to a dog daily for three days, that the sulphur elimination preceded that of the nitrogen, while that of phosphorus followed it. The results of the third day, at a time when the dog was

[1] Addis, T., and Drury, D. R.: J. Biol. Chem., 1923, **55**, 105, 639.
[2] Kast, L., and Wardell, E. L.: Arch. Int. Med., 1918, **22**, 581.
[3] For discussion, see McLean, F. C.: J. Exper. Med., 1915, **22**, 212.
[4] Rubner, M.: "Energiegesetze," 1902, p. 368.

essentially in nitrogen equilibrium, are divided into six hourly periods and are given below:

Period	S Gm.	N Gm.	N/S	Of 100 Per Cent. were Excreted		
				S	N	P
I	0.448	5.57	12.4	**36.7**	24.8	16.0
II	0.387	8.94	23.1	31.7	**39.8**	32.1
III	0.257	5.32	20.7	21.1	23.6	**33.4**
IV	0.131	2.66	20.3	10.5	11.8	18.5
	1.223	22.49	18.4			

The elimination of sulphur more rapidly than nitrogen after meat ingestion in man has been confirmed by von Wendt.[1] It appears that the end-products of the metabolism of sulphur-containing cystin appear in the urine more rapidly than urea, while phosphorus, which is an end-product of nuclein metabolism, makes its appearance more slowly.

Two explanations of the early elimination offer themselves: one, that the sulphur-containing cystin radicle is oxidized with exceptional ease; two, that the sulphur compounds may not accumulate in the organism as does urea. Variations in the rate of sulphur elimination may also undoubtedly be influenced by bacterial activity.

If in man various proteins be added to an already sufficient mixed diet (superposition experiments), the rate of destruction of the added protein as indicated by the extra N eliminated in the urine varies with the character of the protein. Such experiments were first devised by Falta,[2] who established the following classification of proteins in the order of the rapidity of their destruction: *a*, gelatin, casein, serum albumin, fibrin; *b*, blood globulin; *c*, hemoglobin; *d*, egg-albumin. Hämäläinen and Helme[3] continued these experiments and they also investigated the elimination of sulphur and phosphorus. They gave a man weighing 66 kilograms a diet containing 3650 calories and 5 grams of nitrogen. On this diet they superimposed on different days the following amounts of proteins:

800 gm. white of egg = 14.40 gm. N + 1.56 gm. S.
57 gm. proton = 6.94 gm. N + 0.419 gm. S.
320 gm. veal = 13.44 gm. N + 0.832 gm. S.

[1] von Wendt, G.: Skan. Arch. Physiol., 1905, **17**, 211.
[2] Falta, W.: Deut. Arch. klin. Med., 1906, **86**, 517.
[3] Hämäläinen, J., and Helme, W.: Skan. Arch. Physiol., 1907, **19**, 182.

and noticed the time of the elimination of nitrogen, sulphur, and phosphorus through the kidney. It was six days before all the nitrogen of the ingested white of egg was eliminated, whereas that in veal and proton required only two or three days. This is evident from the following table:

DAILY PERCENTAGE ELIMINATION OF THE NITROGEN, SULPHUR, AND PHOSPHORUS OF INGESTED PROTEIN SUPERIMPOSED ON AN ADEQUATE DIET

Day	Egg-white		Proton		Veal		
	N	S	N	S	N	S	P
1	21	41.4	64	90	56	74.2	60
2	21	32.2	10	10	26	17.8	24
3	22	13.4	13	..	18	8.0	16
4	11	4.3	13				
5	14	5.5					
6	11	2.4					

The rapidity of the sulphur elimination is everywhere noticeable. The "nitrogen lag" in the case of white of egg is pronounced and may be due to the retention of "deposit protein" which is only slowly metabolized, and which is poorer in sulphur than the original egg-white.

Mendel and Lewis[1] suggest that the flattened curves of nitrogen elimination found after the ingestion of egg-white or ovalbumin may, to a great extent, be explained by a difference in the rate and completeness of the absorption of these substances when contrasted with the behavior of meat, casein, ovovitellin, edestin, gliadin and gelatin, between which little difference could be observed.

Cathcart and Green[2] have superimposed egg-albumin upon a vegetarian diet in man. In egg-albumin the ratio S:N is 1:8. The S:N of the urine in starvation is 1:15, but after ingesting egg-albumin it was found to be 1:9.8. This indicates a high specific oxidation of sulphur, and leaves a residuum of amino-acids suitable for regrouping into a pabulum of "deposit protein" which is poor in sulphur. It remained to be shown, however, whether such "deposit protein" if metabolized during the early days of fasting would give indication of a low sulphur content.

Wilson[3] gave to a man a basal diet containing 6.4 gm. of protein N for a period of 10 days. He then added to this diet whites of egg

[1] Mendel, L. B., and Lewis, R. C.: J. Biol. Chem., 1913–14, **16**, 75.
[2] Cathcart, E. P., and Green, H. H.: Biochem J., 1913, **7**, 1.
[3] Wilson, H. E. C.: *Ibid.*, 1925, **19**, 322.

containing 10.21 gm. N and 1.059 gm. sulphur, in which the N:S ratio was 9.6:1. Two-thirds of the protein superimposed in the diet was added to the body, and the sulphur retention was of such magnitude as to indicate the production of new muscle tissue from the whites of eggs. The work may be analyzed as follows:

	N in Diet	Urine				
		N:S	N	N above Basal	S	S above Basal 0.456 Gm.
	Gm.		Gm.	Gm.	Gm.	Gm.
Basal diet	6.4	13.6	6.08	....	0.456	
Basal diet + egg-white	16.61	9.1	7.25	1.17	0.791	0.335
Basal diet	6.4	11.1	8.34	2.26	0.747	0.291
Basal diet	6.4	13.6	6.08	....	0.447	
				3.43		0.626

For computing the storage of protein the following equations may be used:

Egg-white N 10.21 gm. in diet *minus* extra N 3.43 gm. in urine = 6.77 gm. N stored in body.

Egg-white S 1.059 gm. in diet *minus* extra S 0.626 gm. in urine = 0.433 gm. S stored in body.

6.77 gm. N: 0.433 gm. S = 15.63:1.

The N:S ratio of protein deposited after taking white of egg is therefore computed to be of the same order as that found by F. G. Benedict and others when body protein is destroyed in fasting (see p. 92). The fecal excretions of N and S were disregarded in the analysis above, but they probably played a minor rôle and would not probably alter the interpretation.

Similar work has been reported by Fay and Mendel.[1] In this case dogs were employed. Fasting 9 and 16 days, one dog showed urinary N: S ratios of 14.1 and 15.6. After giving to another dog a diet free from protein N during 31 days the N: S was 14.0, or about the same as in fasting. When to a third dog a diet was given containing white of egg in which the N: S was 8.6, the urinary N: S was 8.2, showing that there was no tendency of the body to retain the excess of sulphur administered. Finally after a fast of 30 days a complete diet containing casein (N: S = 16.3) was given for 9 days, and the N: S ratio in the urine rose to 41.4 for the period. There was high protein retention and proportionately even higher sulphur retention.

[1] Fay, M., and Mendel, L. B.: Am. J. Physiol., 1925–26, **75**, 308.

Perhaps the depleted fasting cells required not only new functionally active protein, but also in large measure glutathion for their oxidative mechanism.

It may not be beyond the bounds of reason to associate a similar retention of sulphur, probably in the form of glutathion, with the higher oxidative power of growing tissue which characterizes the metabolism of children and of convalescents after wasting disease.

Sherman and Hawk[1] give curves showing beautifully an almost parallel elimination of sulphur and nitrogen in man on a mixed diet. A curve showing this is here presented:

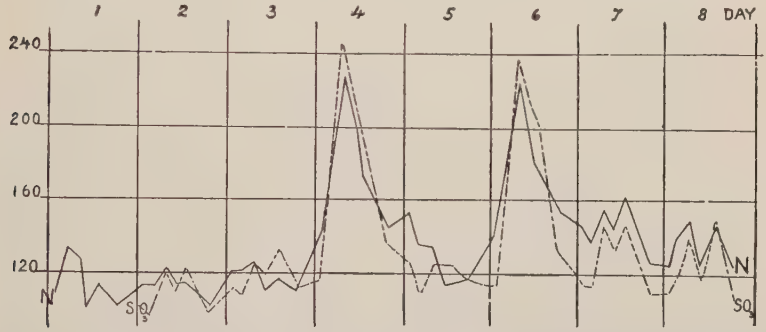


Fig. 14.—The curves here shown represent the relative fluctuations in the average rates of excretion of nitrogen and SO_3. The values on the left represent percentages of an assumed standard rate of excretion for each of these constituents. It will be seen that in general the excretion of sulphates ran quite closely parallel to that of nitrogen.

Wolf[2] presents similar curves after giving veal cutlets or casein to a man. It is evident that the early elimination of sulphur does not always appear. Wolf also describes experiments in which after the ingestion of a liter of raw white of egg by a man the maximal elimination of urinary sulphur followed that of urea by several hours. In this instance the ingesta contained 16.6 grams of nitrogen, and the urine during twenty-four hours only 8.7 grams. This indicates that a large fraction of the protein had a fate which is purely speculative.

If we pass from the consideration of protein metabolism, as indicated by the nitrogen curve, to the consideration of the intermediary metabolism of protein we can see more clearly that the curve of protein nitrogen excretion is not a true index to the sum of the activities contributed to the cells by protein metabolism.

[1] Sherman, H. C., and Hawk, P. B.: Am. J. Physiol., 1900–01, **4**, 43.
[2] Wolf, C. G. L.: Biochem. Z., 1912, **40**, 193, 234.

CHAPTER X

THE INFLUENCE OF PROTEIN FOOD (Continued)

PART II—THE INTERMEDIARY METABOLISM

A reform in our system of preliminary medical training is urgently required—it has long been evident that medicine is but applied chemistry, yet this is in no way recognized notwithstanding the example set by men like Gowland Hopkins and Jacques Loeb.—H. E. Armstrong.

The term "intermediary metabolism" with which so much modern work is intimately associated was used by Bidder and Schmidt on the first page of their celebrated "Verdauungssäfte und Stoffwechsel," published in 1852. Their conception of the breakdown of protein has already been cited.

Voit[1] believed that there was an early cleavage of the protein molecule into a nitrogenous portion and a non-nitrogenous portion, a cleavage involving the liberation of only a small amount of energy; that there was a rapid combustion of the nitrogenous radicle, as shown by the elimination of the nitrogenous end-products in the urine; and that the non-nitrogenous radicle which contained the major part of the potential energy of the protein molecule might in part be temporarily stored either as glycogen or fat and be gradually doled out to the tissues as the need required.

Claude Bernard believed that glycogen could arise from protein. Wolffberg[2] let fowls fast two days to remove the glycogen and then for two days gave meat powder which was free from carbohydrate. Two fowls, killed during the interval of protein digestion, showed considerable glycogen in their livers (1.56 and 1.45 per cent.) and muscles (0.251 and 0.454 per cent.), much more than would have been present in starvation. Two similar fowls, killed seventeen and twenty-four hours after the last protein ingestion, contained much less glycogen in their livers (0.145 and 0.22 per cent.) and muscles (0.211 and 0.162 per cent.). This origin of glycogen from protein was fully confirmed by Külz[3] in a very extended series of experiments

[1] Voit, C.: Z. f. Biol., 1891, **28,** 291.
[2] Wolffberg, S.: *Ibid.*, 1876, **12,** 278.
[3] Külz, E.: "Ludwig's Festschrift," Marburg, 1891, p. 83.

in which chopped meat, fully extracted with warm water, was made the basis of the ingesta. It became evident from these experiments that if sufficient protein were given to an animal, part of the protein carbon could be retained as glycogen.

It has long been believed that sugar arises from protein in diabetes. Kossel,[1] who knew that hexone bases, leucin, and other protein end-products contained six atoms of carbon, first suggested a relation between them and glucose. The theory of the origin of sugar in diabetes from these amino products was strongly advocated by Friedrich Müller.[2] The definite proof of this was afforded by Stiles and Lusk,[3] who gave a mixture of amino bodies prepared by the pancreatic proteolysis of meat to a dog rendered diabetic with phlorhizin. The mixture was free from protein. The nitrogen ingested was entirely eliminated in the urine, and for each gram of such nitrogen 2.4 grams of extra sugar appeared in the urine.

Considerable sugar may originate from protein in the course of its ordinary metabolism. The question arises at what time during the metabolism does this sugar become available for combustion in the organism? This question was answered by an experiment of Reilly, Nolan, and Lusk.[4] These authors gave a fasting phlorhizinized dog 500 grams of meat and collected the urine in two three-hour and one six-hour periods. The results were as follows:

EXCRETION OF GLUCOSE AND NITROGEN BEFORE AND AFTER INGESTING 500 GRAMS OF MEAT IN DIABETES

	Glucose, Gm.	Nitrogen, Gm.	D:N
Preceding three hours	5.96	1.75	3.41
First three hours after feeding	12.43	2.52	4.92
Second three hours after feeding	14.70	3.76	3.91
Third three hours after feeding	11.23	3.85	2.92
Fourth three hours after feeding	11.23	3.85	2.92
Following three hours	6.34	1.78	3.56

The normal fasting relation between glucose and nitrogen changed immediately upon the ingestion of meat. During the first hours more glucose was eliminated than corresponded to the nitrogen in the urine. During the later hours this proportion was reversed. The sugar elimination, therefore, took place decidedly before that of

[1] Kossel, A.: Deut. med. Wchnschr., 1898, **24**, 581.
[2] Müller, F., and Seemann, J.: *Ibid.*, 1899, **25**, 209.
[3] Stiles, P. G., and Lusk, G.: Am. J. Physiol., 1903, **9**, 380.
[4] Reilly, F. H., Nolan, F. W., and Lusk, G.: *Ibid.*, 1898, **1**, 395. For similar work after giving casein, serum albumin, gliadin, and edestin with separation of urine in hourly periods, consult Janney, N. W.: J. Biol. Chem., 1915, **20**, 321.

the nitrogen. This is shown in the following calculation of the percentage elimination of nitrogen and glucose in three-hour periods following the ingestion of 500 grams of meat in the above experiment:

	Glucose, Per Cent.	Nitrogen, Per Cent.
During first three hours	25.06	18.02
During second three hours	29.64	26.90
During third three hours	22.65	27.54
During fourth three hours	22.65	27.54
	100.00	100.00

The relations are represented in the following curve:

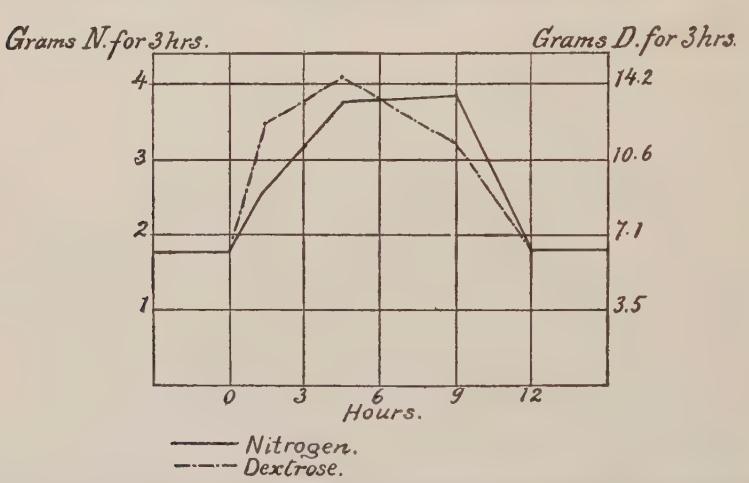


Fig. 15.—Curve showing the elimination of glucose before nitrogen after meat ingestion (500 grams) in diabetes.

That the glucose production from the meat ingested was proportional to the protein destroyed is evident from the following comparison, in which the sum of the glucose and nitrogen eliminated in the twelve hours is considered. Nitrogen and glucose double in quantity after the ingestion of meat, but their ratio remains the same as in starvation.

	Glucose, Gm.	Nitrogen, Gm.	D:N
Fasting twelve hours	23.87	7.00	3.41
After 500 gm. meat, twelve hours	49.59	14.00	3.54
Subsequent twelve hours	25.36	7.11	3.56

The curve shows that there is an early production of sugar from protein which may be liberated in metabolism before the nitrogen belonging to the protein is eliminated in the urine. A similar early

production of sugar from protein has also been observed after feeding dogs with meat in pancreas diabetes.[1]

Since 1 gram of nitrogen in the urine represents a destruction of 6.25 grams of meat protein, and since there is simultaneously an average elimination of 3.65 grams of glucose in phlorhizin diabetes, it may be calculated that the sugar production from meat amounts to 58 per cent. by weight of the meat protein metabolized and may contain 52 per cent. of its total available energy (see p. 670).

Another calculation shows that of the carbon from protein which is ordinarily eliminated in the respiration 57.2 per cent. may pass through the glucose stage (see p. 670).

After the ingestion of protein in the normal organism this sugar early becomes available and may be oxidized before the nitrogen belonging to it is eliminated, or if the sugar be formed in excess, it may be stored as glycogen in the liver and muscles of the body for subsequent use. In this way it is obvious that at least half the energy in protein may be independent of the curve of nitrogen elimination, but may rather act as though it had been ingested in the form of carbohydrate. This will be explained in the next chapter. It is therefore evident that this carbohydrate, which is early supplied in the breaking down of protein, may distribute its energy according to the requirement of the cells as long as it lasts. This is apparently the principal cause of the comparative evenness of the carbon dioxid excretion as contrasted with the great irregularity of the nitrogen elimination after protein ingestion.

Pflüger who, longer than any physiologist, denied the validity of any existing proof that glucose arose from protein, was in his old age ultimately convinced by the following experiments. He[2] found that when dogs were allowed to fast for ten days and then made diabetic by an injection of phlorhizin the glycogen of the liver amounted to 0.1 per cent. and of the muscles to 0.2 per cent. If dogs reduced to this condition were given large quantities of codfish (which contains only 0.03 per cent. glycogen) the glycogen content of the liver averaged 6.5 per cent., and in one case rose to 9.9 per cent., and the glycogen content of the muscle averaged 1 per cent. *Since fat ingestion was without effect upon the glycogen store, Pflüger acknowledged the origin of glucose from protein.*

[1] Berger, A.: Inaugural Dissertation, Halle (Nebelthau), 1901; cited from Maly's Jahresbericht über Thierchemie, 1901, **31**, 848.

[2] Pflüger, E., and Junkersdorf, P.: Pflüger's Arch. gesam. Physiol., 1910, **131**, 201.

It must be borne in mind that it is not very long ago that it was perfectly permissible to think of protein as a complex containing many glucose molecules existing in a highly polymerized condition and combined with nitrogen-containing radicles, of which glycin, leucin, and tyrosin at least were readily obtainable as cleavage products. Such a molecule explained the older conceptions of protein metabolism. The work of Hofmeister, Kossel, and Emil Fischer first gave a true insight into the composition of the protein molecule. One must know the life history of sixteen amino-acids in order to be familiar with the metabolism of protein. Though the extension of knowledge may have been at the cost of simplicity, yet order is being wrought out of apparent complexity. It is often difficult for an older generation to think in terms of the knowledge of a new. The author's father was a student at Heidelberg at the time when the modern chemical formulæ were introduced, when H—O became H_2O, and he recalled the distracted exclamation of one of the university professors, "Ach Gott! wie kann man so lernen!"

The intimate knowledge of the behavior of the amino-acids within the body may be studied by a variety of means.

1. The direct removal in the urine of certain of the amino-acids, such as glycin and cystein, or the removal of slightly changed products, such as homogentisic acid from tyrosin and kynurenic acid from tryptophan.

2. The determination in the urine of a dog made diabetic by phlorhizin of the quantity of "extra glucose" eliminated after the ingestion of certain amino-acids, and the determination of an increase in the quantity of β-oxybutyric acid after the administration of other amino-acids under like conditions. The depancreatized dog may also be employed.

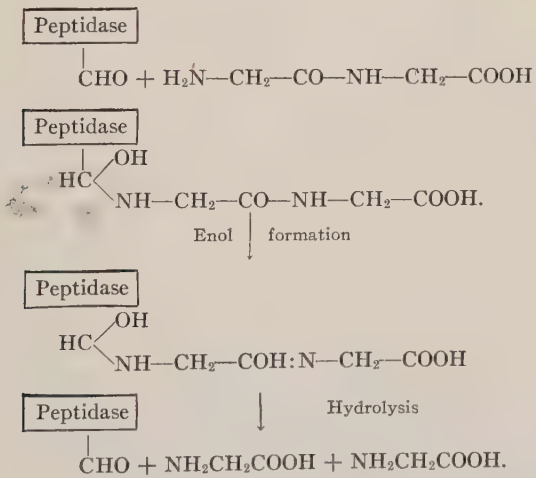
3. The results of experiments in which an amino-acid is added to warmed oxygenated blood and this perfused through a surviving liver, subsequent analysis of the blood revealing any chemical change which the material might have undergone.

It should be remembered that when amino-acids are ingested the resulting nitrogen increase in the urine is entirely due to urea.[1] The same is true of the dipeptid glycyl-glycin[2] (see p. 81). It is believed that the deamination of an amino-acid results in the formation of

[1] Levene, P. A., and Kober, P. A.: Am. J. Physiol., 1908–09, **23,** 324.
[2] Levene, P. A., and Meyer, G. M.: *Ibid.*, 1909–10, **25,** 214.

ammonia, which, becoming ammonium carbonate, may be converted into urea. Yet experiments *in vitro* have failed to demonstrate this action. Gertrude Bostock[1] found that the liver and intestinal mucosa failed to deaminize alanin. Levene and Meyer[2] find that leucocytes and kidney tissue do not deaminize glycin, alanin, aspartic acid, and leucin. Griesbach and Oppenheimer[3] are of the same opinion. The recent work of Bollman, Mann, and Magath[4] has shown apparently that *there is no deamination of protein in the body after the removal of the liver.* For, following this operation on a dog, amino-acids may be recovered in blood, tissues, and urine in magnitude approximately equal to the anticipated formation of urea had the animal been normal. If amino-acids were injected into these animals the whole amount of the amino-acid nitrogen was recovered unchanged in the blood, urine and tissues many hours after hepatectomy. Furthermore, *there was no glucose formation from amino-acids after hepatectomy.* Thus the *characteristic biologic reaction of deamination is effected through the activity of living cells of liver tissue.*

The proteolytic breakdown of the simplest dipeptid glycyl-glycin by the action of intestinal erepsin is thus pictured by Josephson and von Euler:[5]



[1] Bostock, G. D.: Biochem. J., 1911, **6,** 48.
[2] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1913, **15,** 65; 1913–14, **16,** 555.
[3] Griesbach, W., and Oppenheimer, S.: Biochem. Z., 1913, **55,** 329.
[4] Bollman, J. L., Mann, F. C., and Magath, T. B.: Am. J. Physiol., 1926, **78,** 258.
[5] Josephson, K., and von Euler, H.: Z. physiol. Chem., 1926–27, **162,** 85.

A similar influence is supposed to act in the breakdown of longer chains. Protein shattered after this fashion passes in the form of a stream of amino-acids through the portal vein to the liver for deamination. London and his pupils[1] find that during protein digestion the hepatic vein is much richer in polypeptids than is the portal vein. Hence in the intermediary metabolism following protein ingestion one deals, not alone with the free amino-acids absorbed from the intestine, but also with polypeptids synthesized in the liver from the amino-acids of meat. Interesting in this connection is the discovery of Felix and Morinaka[2] in Kossel's laboratory that if arginin be perfused through the liver it is freely split into urea and ornithin, whereas arginin in peptid form is not destroyed by the liver but passes through it unaffected.

One possible inference which may be drawn from the analysis above is that polypeptids formed in the liver must be broken into simple amino-acids elsewhere in the body before they can be deaminized by the liver.

For the understanding of the biochemic relations of the various amino-acids it seems desirable to present as briefly as possible the laws governing their fate in the organism.[3]

THE PROCESS OF DEAMINATION

The nature of the attack of the living cell upon the NH_2 group of the amino-acids has been the subject of much investigation. The process was at first thought to be one of simple hydrolysis, as follows:

$$R—CHNH_2—COOH + HOH = R—CHOH—COOH + NH_3$$

After this fashion glycin $CH_2NH_2—COOH$, would become glycollic acid, $CH_2OH—COOH$; alanin, $CH_3—CHNH_2—COOH$, would become lactic acid, $CH_3—CHOH—COOH$, and so forth.

It was Otto Neubauer,[4] in the laboratories of the second medical clinic of the University of Munich, who first showed that the process of *deamination* might be one of *oxidation* and not hydrolysis. This process of *oxidative deamination* is represented in the following formula:

$$R—CHNH_2—COOH + O = R—CO—COOH + NH_3$$

[1] London, E. S., Kotschneff, N., Kalmykoff, M. P., Schochor, N. J., and Abaschydze, T.: Pflüger's Arch. gesam. Physiol., 1924, **205,** 482.

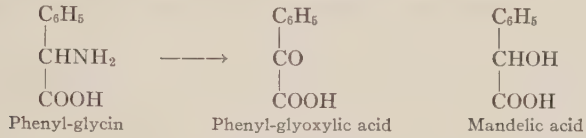
[2] Felix, K., and Morinaka, K.: Z. physiol. Chem., 1924, **132,** 152.

[3] For excellent reviews, see Dakin, H. D.: "Oxidations and Reductions in the Animal Body," 2d ed., London, New York, etc., 1922; Underhill, F. P.: "The Physiology of the Amino Acids," New Haven and London, 1915.

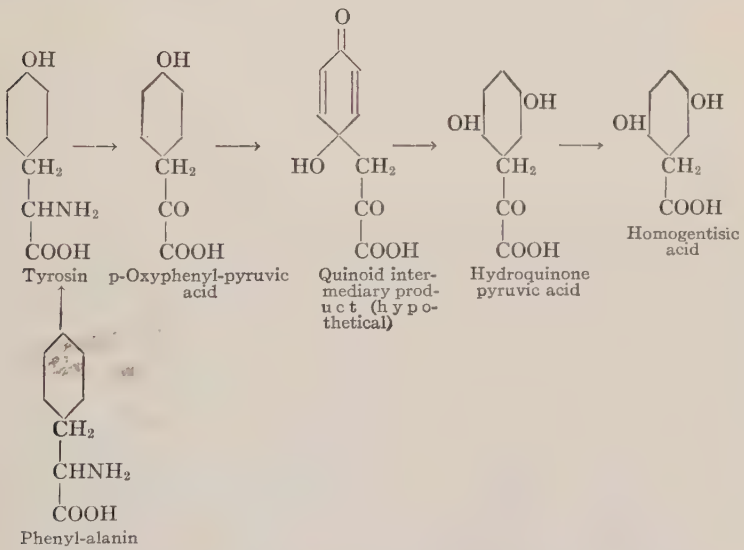
[4] Neubauer, O.: Deut. Arch. klin. Med., 1909, **95,** 211.

From glycin, CH_2NH_2—COOH, one would thus obtain glyoxylic acid, CHO—COOH; and from alanin, CH_3—$CHNH_2$—COOH, pyruvic acid, CH_3—CO—COOH.

That this method of oxidation is actually possible in the organism was evident when Neubauer gave phenyl-glycin to a dog and found phenyl-glyoxylic acid as well as mandelic acid in the urine.



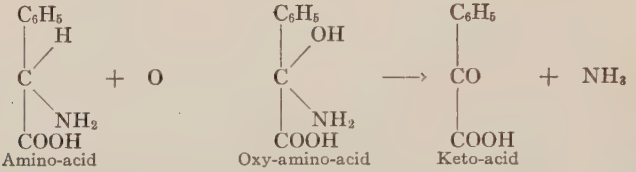
Further evidence was obtained by Neubauer through the medium of a rare anomaly of human metabolism called *alcaptonuria* (see p. 235). In this disease tyrosin and phenylalanin are not oxidized to their usual end-products, but are eliminated in the urine as *homogentisic acid*. The transformation of phenyl-alanin and tyrosin into homogentisic acid is believed to follow the scheme presented below:



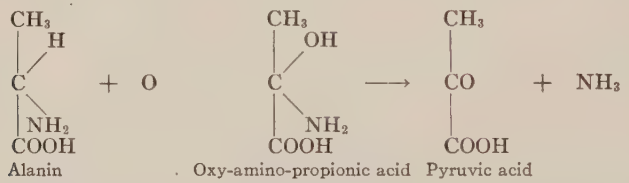
It will be noted that the alanin radicle, CH_2—$CHNH_2$—COOH, is represented as undergoing oxidative deamination, being converted into pyruvic acid. Neubauer drew this conclusion from the fact that if phenyl-alanin, tyrosin, or p-oxy-phenyl-pyruvic acid were given to the alcaptonuric patient they all appeared in the urine as homogentisic acid, whereas when p-oxy-phenyl-lactic acid was given there

was no increase in the homogentisic acid excretion whatever. Consequently it could not have been an intermediary product in the metabolism of tyrosin. Neubauer, therefore, concluded that the primary pathway of deamination was oxidative and not hydrolytic.

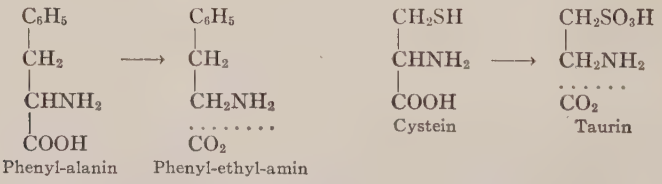
Kotake and his pupils[1] have more recently recovered oxyphenylpyruvic acid in the urine of rabbits to which they had administered 5 and 10 grams of d-l- or l-tyrosin. They regard it as proved that tyrosin undergoes oxidative deamination. Neubauer[2] presented the following formula as indicating the probable reaction of oxidative deamination:



Alanin, for example, would follow this pathway:



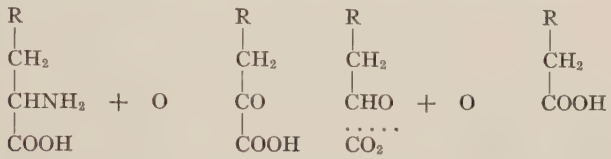
Examination of the formula given for the conversion of phenylalanin into homogentisic acid shows that the alanin radicle of phenylalanin is converted into an acetic acid radicle in homogentisic acid. The question arises whether the first step in the destruction of phenylalanin might not be the loss of its acid group by CO_2 cleavage, as indeed happens when it is acted upon by bacteria,[3] and as is usual in the transformation of cystein into taurin.



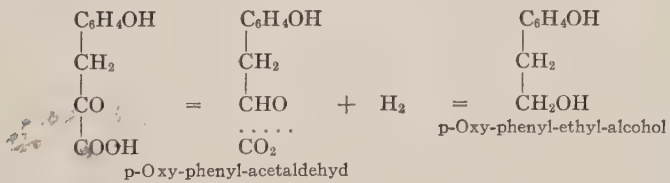
As phenyl-ethyl-amin is poisonous, its first oxidation product, phenyl-ethyl-alcohol, was given by Neubauer to the alcaptonuric,

[1] Kotake, Y., Matsuoka, Z., and Okagawa, M.: Z. f. physiol. Chem., 1922, **122,** 166.
[2] Neubauer, O., and Fromherz, K.: *Ibid.*, 1910–11, **70,** 326.
[3] Spiro, K.: Hofmeister's Beitr. chem. Physiol. u. Path., 1902, **1,** 347.

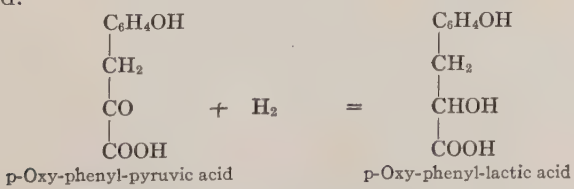
but without increasing the quantity of homogentisic acid. It appeared in the urine as phenyl-acetic acid (paired with glycin). This indicates that oxidative deamination takes place in the metabolism of phenyl-alanin before CO_2 is split from the acid radicle. The CO_2 cleavage follows deamination, as appears in the formula given for the transformation of hydroquinone-pyruvic acid into homogentisic acid. It follows from this that after the oxidative deamination of an amino-acid, the deaminized remainder may be converted into an acid containing one less carbon atom, as follows:



If after producing the aldehyd by CO_2 cleavage, *reduction* prevails instead of oxidation, then an alcohol is formed instead of an acid. This may be illustrated by the work of F. Ehrlich,[1] who found that when yeast acted on tyrosin the end-product was p-oxy-phenyl-ethyl-alcohol, $OH—C_6H_4—CH_2CH_2OH$. Neubauer and Fromherz, continuing their theoretic researches, discovered that yeast acting on p-oxy-phenyl-pyruvic acid yields this same ethyl-alcohol derivative, while p-oxy-phenyl-lactic acid does not give it. Para-oxy-phenyl-pyruvic acid may, therefore, be transformed as follows:



Although p-oxy-phenyl-lactic acid is not acted on by yeast, yet it also appears as a product when yeast acts on p-oxy-phenyl-pyruvic acid. Hence pyruvic acid may be reduced, with the formation of lactic acid.

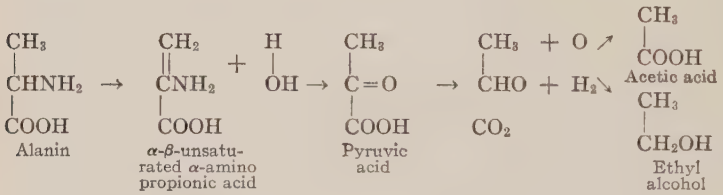


[1] Ehrlich, F.: Ber. deut. chem. Ges., 1907, **40**, 1047.

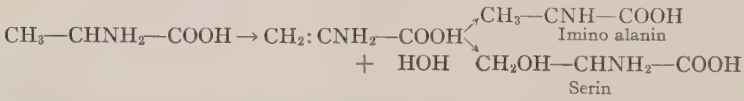
In conformity with this stands the observation of P. Mayer,[1] who found that if pyruvic acid were administered to a rabbit lactic acid appeared in the urine.

Although it appears certain that oxidative deamination is the principal method of attack upon the amino group of the aromatic acids, yet direct hydrolytic deamination has been noted for them, and it may play a considerable rôle in the metabolism of the amino-acids of the aliphatic series as well. Neubauer finds the lævo-component of p-oxy-phenyl-lactic acid in the urine of a patient suffering from cirrhosis of the liver. Since the dextro-component is always eliminated in the human being whenever it is formed by reduction of p-oxy-phenyl-pyruvic acid within the organism, it follows that this latter substance could not have been the intermediary one, but that the l-compound was formed by the direct hydrolytic cleavage of l-tyrosin.

One may summarize the results of Neubauer and introduce into the scheme the primary withdrawal of hydrogen in accordance with the theory of Wieland, if one pictures the fate of alanin as follows:



Alternatives presented by Dakin[2] are as follows:



Both Neubauer's hydroxyalanin and the above mentioned imino acid are hypothetical substances, and both must be chemically highly reactive. The latter, through hydrolysis, would readily be transformed into ammonia and pyruvic acid.

These reactions give one an insight into oxidations, reductions, hydrolyses, and cleavages, which are of constant occurrence as the result of vital activities.

[1] Mayer, P.: Biochem. Z., 1912, **40**, 441.
[2] Dakin, H. D.: J. Biol. Chem., 1926, **67**, 341.

It has been noted by Kotake[1] that although p-oxy-phenyl-pyruvic acid is completely oxidized when administered to a rabbit, p-oxy-phenyl-lactic acid remains almost untouched and appears in the urine. The fact, however, that lactic acid and alanin pass over into sugar much more readily than does pyruvic acid leads Ringer[2] to believe that the metabolism of alanin probably follows the path of hydrolytic deamination into lactic acid rather than that of oxidative deamination into pyruvic acid.

The reader should realize that there are many possible pathways in metabolism, and the representations given above may be regarded as suggestive rather than literally exact.

THE OXIDATION OF FATS

In order to be able to understand the further fate of some of the deaminized remainders of the amino-acids, the method of oxidation of fatty acids must be understood. The experiments of Knoop[3] are based on the fact that benzoic acid, C_6H_5COOH, when given to an animal pairs with glycin and appears as hippuric acid in the urine, whereas phenylacetic acid, $C_6H_5CH_2COOH$, when given pairs in the same way and is eliminated as phenaceturic acid. Knoop found that whenever aromatic derivatives of the fatty acids were given to an animal one of these two forms always appeared in the urine; that if the side chain had an odd number of carbon atoms hippuric acid was always the end-result, and if there were an even number of atoms phenaceturic acid appeared as the final product.

The following substances were given:

$C_6H_5—CH_2—CH_2—CH_2—CH_2—COOH$ Phenylvalerianic acid.

$C_6H_5—CH_2—\overset{\beta}{CH_2}—CH_2—COOH$ Phenylbutyric acid.

$C_6H_5—\overset{\beta}{CH_2}—CH_2—COOH$ Phenylpropionic acid.

Since phenylvalerianic and phenylpropionic acids both yielded hippuric acid and phenylbutyric did not, it was evident that the last named was not an intermediary product between the first two. Knoop, therefore, concluded that in the oxidation of fats the β-carbon atom was oxidized and that two carbon atoms dropped from the chain together. This view was supported by Dakin's[4] discovery

[1] Kotake, Y.: Z. physiol. Chem., 1910, **69**, 409.
[2] Ringer, A. I.: J. Biol. Chem., 1913, **15**, 145.
[3] Knoop, F.: Hofmeister's Beitr. chem. Physiol. u. Path., 1905, **6**, 150.
[4] Dakin, H. D.: J. Biol. Chem., 1909, **6**, 203.

that when phenylpropionic acid was given in large amounts phenyl-β-oxy-propionic acid, $C_6H_5—CHOH—CH_2—COOH$, was detected in the urine. Corroborative evidence is further found in the fact that when body fat or food fat, both of which always contain an even number of carbon atoms, are metabolized in the diabetic, the end-product is always β-oxybutyric acid, $CH_3CHOHCH_2COOH$, which one would expect in terms of the theory.

It is interesting to note the results of giving the following three substances:

$$\begin{array}{lcl} C_6H_5COCH_2COOH & \longrightarrow & C_6H_5COOH \\ C_6H_5CH_2COCOOH & \longrightarrow & \text{oxidized} \\ C_6H_5COCH_2CH_2COOH & \longrightarrow & C_6H_5CH_2COOH \end{array}$$

Phenyl-β-keto-propionic acid is oxidized on the β-carbon atom to benzoic acid. Phenyl-α-keto-propionic acid (phenyl-pyruvic acid), as stated, is completely oxidized in the organism, while phenyl-γ-keto-butyric acid undergoes reduction of its γ-carbon and oxidation of its β-carbon and is eliminated in the urine as phenyl-aceturic acid. Here reduction and oxidation play alternately upon the same molecule. No satisfactory chemical reason has ever been advanced in explanation of the reason why phenyl-pyruvic acid is the only compound of this unsubstituted series which the animal can oxidize.

Clutterbuck and Raper[1] have demonstrated the improbability of oxidation on the γ-carbon atom by investigating the fate of phenylsuccinic acid and β-phenylhexoic acid in the animal body. The first substance,

$$\begin{array}{l} \qquad C_6H_5 \\ \qquad\quad | \\ HOOC—CH—CH_2—COOH, \end{array}$$

is eliminated largely unchanged in the urine, and the second substance,

$$\begin{array}{l} \qquad\qquad\qquad C_6H_5 \\ \qquad\qquad\qquad\quad | \\ CH_3—CH_2—CH_2—CH—CH_2—COOH, \end{array}$$

is also so eliminated. The β-carbon atom of the second substance is bound, preventing oxidation at that point, and the γ-δ- and ϵ-carbon atoms remain untouched.

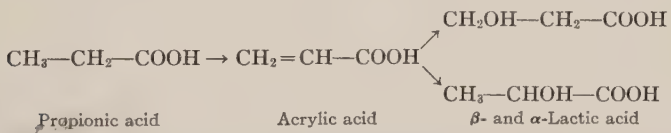
The oxidation of *unsaturated fatty acids*, or such as have a double linkage between two carbon atoms, follows the same laws as the oxidation of saturated fatty acids. Thus, Erdmann and Marchand[2] found that if cinnamic acid, $C_6H_5.CH:CH.COOH$, be given to an

[1] Clutterbuck, P. W., and Raper, H. S.: Biochem. J., 1925, **19**, 911.
[2] Erdmann and Marchand: Liebig's Ann. Chem u. Pharm., 1842, **44**, 344.

animal, hippuric acid appears in the urine. Dakin[1] administered the material in large doses to cats and found the intermediary oxidation product, phenyl-β-oxy-propionic acid, $C_6H_5.CHOH.CH_2COOH$, in the urine.

This preliminary discussion has shown that amino-acids are oxidized at the α-position which is the point of attachment of the NH_2 group, and are converted into oxy- or keto-acids and then into acids having one less carbon atom. After this the organic acid becomes subject to the laws of β-oxidation, under which a fatty acid is oxidized on its β-carbon atom, oxy- and keto-acids being first formed, and then there is cleavage of two carbon atoms with the formation of an acid which contains two less carbon radicles than before. Frequently β-oxybutyric acid is an intermediary product of this oxidation, just as happens in the case of fatty acids. In other cases in which the product contains three atoms of carbon, the end-product may be converted into glucose in the organism. Ringer[2] has demonstrated that in the β-oxidation of fatty acids having uneven numbers of carbon atoms sugar is formed from them in the diabetic organism in proportion to the power to produce propionic acid, $CH_3.CH_2.COOH$. This might form β-lactic acid, $CH_2OH.CH_2COOH$, which, in turn, might be converted into glucose.

A more modern interpretation is given by Dakin[3] to accord with the principles of Wieland's theory of oxidation.



Acrylic acid, fed to a phlorhizinized dog, is converted into glucose. Nothing definite is known regarding the chemistry of the oxidation of acetic acid (see p. 390).

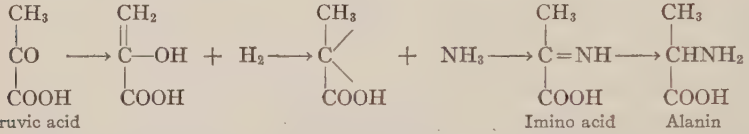
THE SYNTHESIS OF AMINO-ACIDS IN THE BODY

Knoop and Oesterlin[4] have studied the artificial production of amino-acids by laboratory methods which are believed to approximate conditions existing in the body. Knoop has produced α-

[1] Dakin, H. D.: "Oxidations and Reductions in the Animal Body," New Haven and London, 2d ed., 1922, p. 48.
[2] Ringer, A. I.: J. Biol. Chem., 1913, **14**, 43.
[3] Dakin, H. D.: *Ibid.*, 1926, **67**, 341.
[4] Knoop, F., and Oesterlin, H.: Z. physiol. Chem., 1925, **148**, 294.

amino butyric acid from phenyl-α keto-butyric acid, ammonia, and hydrogen in the presence of palladium. A yield of 66 per cent. of the theoretical was recovered. Phenyl-pyruvic acid under like conditions yielded phenyl-alanin, and α-ketoglutaric acid gave glutamic acid. β- and γ-keto acids could not be converted into amino-acids. Under the conditions described amino-acids are formed much more readily than hydroxy-acids.

The reaction in the keto-acid, ammonia, hydrogen system takes place also when methyl-amin $CH_3—NH_2$ is substituted for ammonia, but not when dimethyl-amin $(CH_3)_2NH$ is used. It follows therefore that the group $=N—$ with a free double bond is essential. This indicates the production of an intermediary imino acid.



Writing in 1925, Knoop says that "the readiness of the reaction between ammonia and the keto-acids of the α-series makes it probable that this is the way of the amino-acid synthesis. It also offers an explanation of the necessity for urea in the animal body. For even though amino-acid synthesis plays only a moderate rôle in the body, yet because it represents a reversible equilibrium reaction, it is necessary that the ammonia ions be constantly removed. This is accomplished by their transformation into urea."

In 1926[1] he is more emphatic and writes that it is wrong to think that the reaction, α-keto-acid + NH_3 = amino-acid, is of no importance in the body. "I hold it very probable," he says, "that reversible reactions take place much more often than is at present thought, indeed I think they are of dominating importance though at the present moment we are unable to visualize them."

In this later paper he notes that he has let cystein, α-keto-acid and ammonia react together and has produced amino-acid.

THE INTERREACTION OF AMINO-ACIDS WITH TRIOSE MOLECULES

Knoop and Kertess[2] made the observation that after giving γ-phenyl-α-keto-butyric acid an acetylated amino-acid was recovered in the urine.

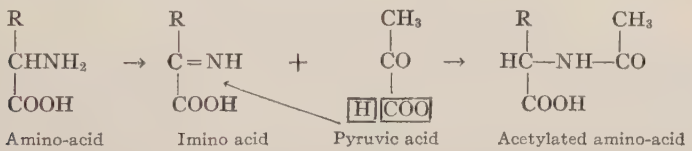
[1] Knoop, F.: Münchener med. Wochenschr., 1926, **73**, 2151.
[2] Knoop, F., and Kertess, E.: Z. physiol. Chem., 1911, **71**, 252.

$$C_6H_5—CH_2—CH_2—CO—COOH \rightarrow C_6H_5—CH_2—CH_2—\underset{\displaystyle NH\\ \displaystyle COCH_3}{CH}—COOH$$

Knoop and Blanco[1] later administered 6 gm. of i-phenyl-amino-butyric acid and found the acetylated d-compound in the urine. The amount in the urine was slightly increased when pyruvic acid was given at the same time, but there was no increase after giving acetic acid or butyric acid.

Curiously enough, Harrow, Power, and Sherwin[2] report that after giving 1 gm. of p-amino-benzoic acid to rabbits the amount of p-acetyl-amino-benzoic acid excreted in the urine is largely increased when sodium acetate and aceto acetic acid are administered at the same time, is somewhat increased after giving pyruvic acid, glycerol, and glyceric aldehyd, but is not at all increased after giving glucose, fructose, and sucrose.

The interpretation of acetylation as given by Knoop is represented in the following formula:



Hydrolysis would convert the acetylated amino-acid into acetic acid and the original amino-acid. The reactive imino acid brings about the partial oxidation of pyruvic acid, a strong acid, which is commonly assumed to be a product of carbohydrate metabolism.

Knoop explains that the formation of imino acids through dehydrogenization produces hydrogen acceptors of high potentiality which have the power to oxidize other materials. When d-iminophenyl-butyric acid meets pyruvic acid in the body it reacts with it and an acetylated compound is formed. It has time to do this before its own destruction because in the d-form it is an imino acid which is foreign to the body and it remains in the imino form long enough to become acetylated. The acetylation of cystein after its union with brombenzol is due to an analogous delay.

However, Knoop has come to believe that the acetylation of amino-acids is a normal process and is the explanation on purely chemical grounds of the sparing action of carbohydrates on protein

[1] Knoop, F., and Blanco, J. G.: Z. physiol. Chem., 1925, **146**, 267.

[2] Harrow, B., Power, F. W., and Sherwin, C. P.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 422.

metabolism. For example, the acetylation of alanin in the presence of pyruvic acid might be performed several times.

When we come to consider the phenomenon of the specific dynamic action of amino-acids we will encounter difficulties in accepting the belief in (1) the origin of amino-acids *de novo* in the normal animal and (2) the repeated use of amino-acids as catalyzing agents.

Experiments have shown that the glucose-forming amino-acids include glycin, alanin, prolin, aspartic and glutamic acids, serin, cystin, and arginin. Some of the other amino-acids yield β-oxybutyric acid as an intermediary product.

It seems desirable at this point to enter into the more intimate details of the life-history of the different amino-acids. Though the general energy metabolism may be understood without this knowledge, yet the finer comprehension of the subject cannot be otherwise obtained.

THE FATE OF THE AMINO-ACIDS

Glycin ($CH_2NH_2.COOH$).—*Probably both carbon atoms are able to enter into the formation of glucose. Present in most proteins; in beef* 4 *per cent.; in large amount* (26 *per cent.*) *in gelatin; absent in milk proteins and in gliadin of wheat. Formerly called glycocoll.*

It has been noted that when benzoic acid is administered to an animal it forms a synthetic compound with glycin within the organism which is eliminated in the urine as hippuric acid.

$$C_6H_5.COOH + CH_2.NH_2.COOH = C_6H_5CO.NHCH_2.COOH + H_2O$$

Hippuric acid is found in the urine of horses and cattle in the food of which materials convertible into benzoates are found. In man Blatherwick and Long[1] find that the increased urinary acidity produced by eating prunes and cranberries is due to an analogous production of hippuric acid. After the ingestion of 450 gm. of prunes the hippuric acid excretion in the urine rose from 1 gm. to 10 gm. per day. After taking 305 gm. of cranberries the hippuric acid excretion was about half that caused by an equal weight of prunes. It is eliminated almost as soon as it is formed, for Lewis[2] found after administering hippuric acid to a man that 82 per cent. could be recovered in the urine within three hours.

[1] Blatherwick, N. R., and Long, M. L.: J. Biol. Chem., 1923, **57**, 815.
[2] Lewis, H. B.: *Ibid.*, 1914, **18**, 225.

Lewinski[1] found that when 10 or 20 grams of benzoic acid were administered to a man in the form of sodium benzoate the entire quantity of benzoic acid was combined and eliminated in the form of hippuric acid. Only when the power to form glycin was exceeded was there an elimination of benzoic acid. Thus, after giving 50 grams of benzoic acid, 62.3 grams of hippuric acid containing 42.3 grams of combined benzoic acid were eliminated, together with 8.2 grams of uncombined acid.

The following data are taken from Lewinski's experiments upon the same individual when partaking of low and of high protein diets. The figures are for twenty-four hours:

Benzoic Acid Administered Grams	Total N in Urine Grams	Hippuric Acid N Grams	HN TN
25	9.3	2.74	29.4
40	9.0	3.15	34.9
40	23.7	4.06	18.0
50	29.1	4.87	18.6

When there were 9 grams of total nitrogen eliminated, 3.15 grams or 35 per cent. appeared in the form of glycin. When 29 grams of total nitrogen, only 4.87 grams of nitrogen appeared in the form of glycin. In other words, an increase of 20 grams of nitrogen in the urine was accompanied by an increase of 1.72 grams of glycin nitrogen, which is only 8.5 per cent. of the increase in protein metabolism instead of 35 per cent.

Magnus-Levy[2] found that 25 to 27 per cent. of the total urinary nitrogen of rabbits fed with cream and of a goat fed with hay is excreted in the form of hippuric acid when benzoate of soda is administered with the food. He calculated that only 4 per cent. of this could have been derived from glycin preformed in the protein metabolized, but that 20 per cent. could have originated from leucin did this pass through a glycin stage.

It has already been stated that the individual amino-acids lose their nitrogen as the first step in their metabolism. Only by the union of its nitrogen atom with benzoic acid is glycin spared this fate. One might believe that other amino-acids might unite with benzoic acid in a similar fashion, and then be converted into hippuric acid by oxidation of the rest of their carbon chains. To test this hypothesis,

[1] Lewinski, J.: Arch. exper. Path. u. Pharm., 1908, **58**, 397. See also Dakin, H. D.: J. Biol. Chem., 1909–10, **7**, 103.

[2] Magnus-Levy, A.: Münchener med. Wchnschr., 1905, **52**, 2168.

Magnus-Levy[1] administered subcutaneously benzoylated compounds of alanin, valin, leucin, phenylalanin, aspartic acid, glutamic acid, ornithin, and serin. He found that these compounds were not changed into hippuric acid in the organism, but were eliminated unchanged in the urine.

These experiments were a further demonstration that in the breaking down of amino-acids deamination is the first step, and they leave no conclusion open other than that *glycin arises by a synthetic process.*

The nature of the process is still a riddle. The great elimination of glycin in hippuric acid has been repeatedly observed by Wiechowski[2] and by Ringer,[3] the latter finding that 38 per cent. of the total nitrogen may be eliminated as hippuric-acid nitrogen in the fasting goat. Parker and Lusk[4] suggested the synthetic origin of glycin, but reported that carbohydrates had no influence on the excretion of hippuric acid. Abderhalden and Strauss[5] gave a hog which was nourished on bran and potatoes 12 grams of sodium benzoate daily, and during certain periods added glycin, alanin, and ammonium carbonate. The results were as follows:

Period	No. of Days	Added to Food	Hippuric Acid in Urine 24 Hours Gm.
V	8	....	2.54
VI	8	Glycin, 12 g.	4.51
VII	6	....	3.30
VIII	12	Alanin, 12 g.	3.30
IX	6	....	2.63
X	18	Ammonium carbonate, 15.6 g.	2.20

From this it appears that glycin when given with the benzoate is far from being completely removed in the urine, and that neither alanin which yields ammonia on deamination nor ammonium carbonate itself has any effect whatever on the elimination of glycin.

McCollum and Hoagland[6] have reported some remarkable experiments. A hog, weighing 46.7 kilograms, was brought into a condition of minimal nitrogen metabolism by giving a diet of starch containing 75 calories for each kilogram of body weight. The diet

[1] Magnus-Levy, A.: Biochem. Z., 1907, **6**, 541.
[2] Wiechowski, W.: Hofmeister's Beitr. chem. Physiol. u. Path., 1906, **7**, 204.
[3] Ringer, A. I.: J. Biol. Chem. 1911-12, **10**, 327.
[4] Parker, W. H., and Lusk, G.: Am. J. Physiol., 1899–1900, **3**, 472.
[5] Abderhalden, E., and Strauss, H.: Z. physiol. Chem., 1914, **91**, 81.
[6] McCollum, E. V., and Hoagland, D. R.: J. Biol. Chem., 1913–14, **16**, 299. See also Lewis, H. B.: *Ibid.*, 1914, **18**, 225.

was then continued and increasing amounts of benzoic acid were added. Finally, hydrochloric acid and benzoic acid were given together. The results of the urinary analyses are here reproduced:

Period	No. of Days	Food	Total N Gm.	Urea N Gm.	NH_3-N Gm.	Creatinin N Gm.	Other N* Gm.
I	12	Starch, 75 cal. per kg. alk. salts..	2.56	1.43	0.21	0.488	0.424
II	4	Same + 4 g. benzoic acid.....	2.63	1.29	0.21	0.456	0.681
III	7	Same + 10 g. benzoic acid.....	2.23	0.58	0.22	0.484	0.948
IV	5	Same + 16 g. benzoic acid.....	2.86	0.55	0.38	0.437	1.492
V	5	Starch same, neut. salts + 16 g. benzoic acid + 10 g. 25 per cent. HCl.....	4.03	0.54	1.44	0.424	1.632

* This includes hippuric acid.

It is evident from this that when the protein metabolism is reduced to a minimal level by carbohydrate ingestion (see p. 355) the addition of benzoic acid does not affect the creatinin output, scarcely affects the total nitrogen elimination, but may reduce the total elimination of urea nitrogen from 56 per cent. of the total nitrogen output to 19 per cent. of the total. This difference, or 37 per cent., of the total nitrogen which is ordinarily converted into urea is under these circumstances eliminated as glycin. It is of great significance that this is accomplished without materially changing the amount of protein metabolism (see p. 362). Giving hydrochloric acid with benzoic acid greatly increases ammonia formation, but scarcely influences the other urinary constituents (see p. 262). The urea elimination remains at its former minimal level.

These results have been confirmed in general by Shiple and Sherwin[1] who have shown that giving 3 to 10 gm. of benzoic acid to man does not increase the "wear and tear" protein metabolism. It seems curious that benzoic acid at the minimal level of protein metabolism does not increase such metabolism.

This discussion has shown that one may compute that 35, 37, and 38 per cent. of the total endogenous protein metabolism of man, goat, and pig may pass through a glycin stage and be eliminated in the urine. It is certain that no protein contains this quantity of glycin. In spite of all the work accomplished there is no solution of the problem from what materials this synthetic production of glycin occurs. It arises as does creatinin without having as yet betrayed the secret of its origin. The synthetic production of glycin is of undoubted value

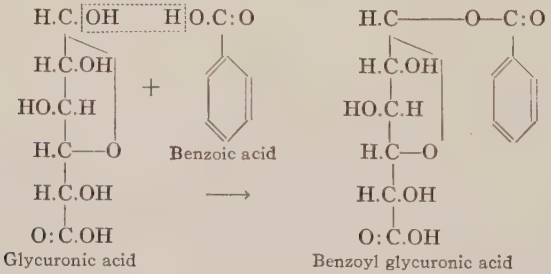
[1] Shiple, G. J., and Sherwin, C. P.: J. Am. Chem. Soc., 1922, **44**, 618.

in making possible the development of body tissue which contains glycin from milk proteins which are free from it.

Cohn[1] was the first to note that when gelatin, a protein rich in glycin, was given to a rabbit at the same time as sodium benzoate, an increased excretion of hippuric acid followed, while no change occurred when casein, which is free from glycin, was administered. This work has been confirmed and extended by Griffith and Lewis,[2] who administered 1 gm. of benzoic acid per kilogram to rabbits and collected the urine for 6 hours. The rate of hippuric acid excretion was notably increased after giving glycin or gelatin or elastin, which are rich in glycin, but was not changed when casein and egg albumin, which are free from glycin, were given. The amino-acids, alanin, cystin, leucin, valin, and aspartic acid, did not increase the output of hippuric acid, nor did glycollic acid, glycol-aldehyd, glucose, urea, or sodium acetate.

Although it is certain that the body has the power to synthesize glycin, the method of its production is profoundly obscure.

Csonka,[3] working with a hog, was the first to emphasize the fact that when benzoic acid is given to this animal it is combined not only with glycin but also with glycuronic acid. Griffith[4] later found similar facts regarding the rabbit.



Csonka discovered that when he gave 16 gm. of benzoic acid to a hog maintained upon a diet of corn-starch, salts, and yeast vitamin, the elimination of hippuric acid was not greatly increased on adding variable amounts of casein to the diet. The percentage of benzoic acid combined as hippuric acid rose from 60, when a pure starch diet was taken, to 68, when casein was added in different quantities.

[1] Cohn, R.: "Festschrift für M. Jaffé," Braunschweig, 1901, p. 321.
[2] Griffith, W. H., and Lewis, H. B.: J. Biol. Chem., 1923, **57**, 1.
[3] Csonka, F. A.: *Ibid.*, 1924, **60**, 545.
[4] Griffith, W. H.: *Ibid.*, 1926, **69**, 197.

The amount of glycin used in hippuric acid formation when no preformed glycin is offered in the food is limited and originates partly from catabolized body protein and partly from synthesis. When the maximum production has been reached there is no difference in the amount of hippuric acid formation either after increasing the casein nitrogen in the diet or after increasing the dose of benzoic acid from 16 to 24 gm. When 16 gm. of benzoic acid are given nearly all the remainder, which is not conjugated with glycin, is conjugated with glycuronic acid. Csonka states that, of the total benzoic acid eliminated in the urine, between 97 and 99 per cent. is in the conjugated form.

When instead of casein, gelatin was the protein administered to the hog, the quantity of hippuric acid formed was increased at the expense of a compensatory decrease in the amount of benzoyl-glycuronic acid eliminated. Ninety per cent. of the benzoic acid was then conjugated with glycin. Hippuric acid N was eliminated to the extent of 1.5 gm. daily, though the gelatin given on different days contained 0.9, 1.9, and 3.7 gm. preformed glycin N. When the smallest amount was given, sufficient glycin originated by synthesis to raise the total output to the same level as when an excess was administered. One of Csonka's tables is here reproduced.

THE VARIATION IN THE QUANTITY OF PROTEIN AS A FACTOR IN HIPPURIC ACID PRODUCTION WHEN 16 GM. OF BENZOIC ACID ARE GIVEN DAILY TO A HOG MAINTAINED WITH A DIET OF CORN-STARCH

Date	In Diet			Urinary output				
					Benzoic Acid Combined			
	Protein	Total N	Glycin N in Gelatin	Glycuronic Acid	With Glycuronic Acid	With Glycin	Hippuric Acid	Hippuric Acid N
1923–24		Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Nov. 19	Casein.	12.32	0	6.60	4.15	9.09	13.34	1.043
Dec. 10	"	6.16	0	7.35	4.63	10.54	15.46	1.209
" 11	"	4.19	0	8.04	5.06	9.52	13.97	1.093
" 12	"	2.09	0	8.05	5.07	8.92	13.08	1.023
" 13	None.	.....	0	7.98	5.02	7.70	11.30	0.884
Mar. 31	Gelatin.	2.97	0.93	3.09	1.95	12.59	18.47	1.445
Apr. 1	"	5.94	1.87	2.78	1.75	13.73	20.15	1.540
" 2	"	11.88	3.74	2.49	1.57	13.39	19.65	1.536
" 4	None.	.....	0	5.50	3.73	11.11	16.30	1.274
" 5	"	.....	....	8.01	5.04	8.77	12.87	1.006

Csonka describes how the growing hog, when given starch and casein containing 6.1 gm. of nitrogen, eliminates only 2.1 gm. in the daily urine, whereas when benzoic acid is also given the urinary nitrogen rises to 4.2 gm. per day. This increase, however, does not take place if glycin be administered in sufficient quantity to unite with benzoic acid. Benzoic acid in the presence of glycin becomes harmless.

Csonka raised the dose of benzoic acid given to the hog from 16 to 24 gm. when the animal was taking starch and casein and witnessed toxic symptoms such as vomiting and nervousness. Urinary analysis indicated that 6.6 gm. of benzoic acid had been retained in the body. The hog refused both food and water, and blindness developed. The administration of 10 gm. of gelatin in 500 c.c. of milk restored the hog to health, and after two days the blindness disappeared. When gelatin was given the hog tolerated 24 gm. of benzoic acid without showing any evidence of distress.

Clementi[1] describes *hippicuricase* occurring in hog's liver which has the power to hydrolyze hippuric acid. Confirming Pribram[2] and Wiechowski,[3] Csonka finds that 10 gm. of hippuric acid administered *per os* to a hog is completely eliminated in the urine as such. If it had been split into its constituent parts a part of the benzoic acid would surely have appeared in the urine conjugated with glycuronic acid. Neither intestinal ferments nor liver hippuricase can therefore split hippuric acid in the hog.

Glycin forms sugar in the organism. Ringer and Lusk[4] found that it was completely converted into glucose in the phlorhizinized dog.

The method employed is to give to a dog, rendered diabetic by phlorhizin and then almost glycogen free by shivering, the material to be tested, and to observe the increased output of glucose in the urine. One may give glucose itself and witness its complete elimination,[5] as follows:

Period	Glucose Gm.	Nitrogen Gm.	D:N	Extra Glucose Gm.
Preliminary	.....	....	3.68	
Glucose, 16 g	25.92	2.87	9.03	15.43
After period	.....	....	3.54	

[1] Clementi, A.: Atti R. Accad. Lincei, 1923, **32**, 2, 172.
[2] Pribram, E.: Arch. exper. Path. u. Pharm., 1904, **51**, 372.
[3] Wiechowski, W.: Beitr. chem. Physiol. u. Path., 1906, **7**, 204.
[4] Ringer, A. I., and Lusk, G.: Z. physiol. Chem., 1910, **66**, 106.
[5] Taken from Csonka, F. A.: J. Biol. Chem., 1915, **20**, 543.

There were 2.87 grams of nitrogen in the urine of seven hours. Assuming the customary D:N = 3.65:1 (see p. 209), then the quantity of glucose derived from the metabolism of protein during the seven hours would be $2.87 \times 3.65 = 10.48$ grams. Deducting 10.48 grams from 25.92 grams found in the urine, it appears that 15.44 grams of extra sugar were eliminated during the period of experimentation.

In the case of glycin the results may be thus analyzed:

Period	Glucose Gm.	Nitrogen Gm.	D:N	Extra Glucose Gm.
Preliminary	.....	.....	3.40	
Glycin, 20 g	47.42	12.84	3.69	16.63
After period	.....	.....	3.37	

During a period of fourteen hours following the ingestion of 20 grams of glycin containing 3.73 grams of nitrogen 12.84 grams of nitrogen appeared in the urine. The difference or 9.11 grams represents the nitrogen of the protein metabolism. Multiplying this by the prevailing D:N = 3.38, one obtains $9.11 \times 3.38 = 30.79$ grams of glucose which could have arisen from the protein metabolism of the time. Since 47.42 grams were actually eliminated, it follows that the difference or 16.63 grams of glucose derived their origin from glycin.

The reaction showing this conversion of glycin into glucose may thus be written, carbon dioxid being neutralized by ammonia liberated from glycin and the compound converted into urea.

$$6C_2H_5NO_2 + 3CO_2 + 3H_2O = 2C_6H_{12}O_6 + 3CH_4N_2O + 3O_2$$
20 g. glycin = 16 g. glucose + 8 g. urea + 4.26 g. O_2

It should be noted that Cremer[1] believes that only three-quarters of the carbon passes over into glucose and holds the following reaction to be the more probable:

$$4C_2H_5NO_2 = C_6H_{12}O_6 + 2CH_4N_2O$$
20 g. glycin = 12 g. glucose + 8 g. urea

By what method may this reaction be accomplished? It has been shown that deamination may result in the formation of either glyoxylic acid, CHO.COOH, or glycollic acid, $CH_2OH.COOH$. These materials must be reduced if they are to form glucose.

[1] Cremer, M.: Med. Klin., 1912, **8**, 2050.

Haas[1] could find no evidence of reduction of glyoxylic to either glycollic or acetic acid in the organism, nor was glycin formed synthetically from it by union with ammonia. Nor could Honjio[2] find any indication of acetic acid formation after perfusing a liver with glycollic acid. Also, the synthesis of glycollic acid into glycin in the organism cannot be accomplished.[3]

If glycollic acid be the product of deamination, as appears most probable, its first reduction product would be glycol-aldehyd.

$$CH_2OH.COOH + H_2 = CH_2OH.CHO + H_2O$$

Glycol-aldehyd in aqueous solution is polymerized with the formation of sugar,[4] $C_6H_{12}O_6$. If administered by subcutaneous injection to a rabbit it leads to an output of sugar in the urine.[5] When perfused through the liver of a tortoise[6] or of a dog[7] glycol-aldehyd is converted into glycogen. If glycol-aldehyd be slowly administered to phlorhizinized dogs, as much as 75 per cent. may escape oxidation and be converted into glucose.[8]

Greenwald[9] suggests that glycin is converted into an amino-aldehyd, this to glycol-aldehyd which passes into glucose.

It is suggestive in this connection to remember that Neuberg[10] has shown that yeast zymases may reduce this simplest of all the oxy-aldehyds into ethylen glycol:

$$\begin{array}{l} CHO \\ | \\ CH_2OH \end{array} \qquad \begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array}$$

But with all our knowledge no one really knows the intermediary breakdown of glycin. If one did it would solve many problems.

It has been stated by Lewis[11] that the *tolerance* for glycin when injected intravenously into a dog is 0.2 gm. per kg. per hour as against 0.85 gm. for glucose.

Hydrazin, which poisons the liver, prevents the metabolism of glycin and the formation of glucose from it.[12]

[1] Haas, G.: Biochem. Z., 1912, **46,** 298.
[2] Honjio, K.: *Ibid.*, 1914, **61,** 286.
[3] Sassa, R.: *Ibid.*, 1914, **59,** 353.
[4] Neuberg, C., and Rewald, B.: Emil Abderhalden's "Biochemisches Handlexikon," Berlin, 1911, **2,** p. 266.
[5] Mayer, P.: Z. physiol. Chem., 1903, **38,** 152.
[6] Parnas, J., and Baer, J.: Biochem. Z., 1912, **41,** 392.
[7] Barrenscheen, H. K.: *Ibid.*, 1914, **58,** 300.
[8] Sansum, W. D., and Woodyatt, R. T.: J. Biol. Chem., 1914, **17,** 521.
[9] Greenwald, I.: *Ibid.*, 1918, **35,** 461.
[10] Neuberg, C.: Biochem. Z., 1915, **71,** 1.
[11] Lewis, J. H.: J. Biol. Chem., 1918, **35,** 567.
[12] Lewis, H. B., and Izume, S.: *Ibid.*, 1926–27, **71,** 33.

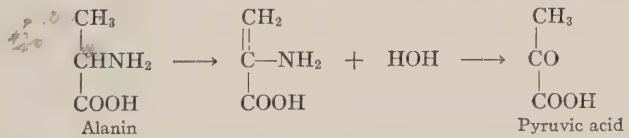
The power to synthesize hippuric acid has been used as a *test of renal function in man.* Morgulis, Pratt, and Jahr[1] state that in normal persons, when 2.4 gm. of sodium benzoate (= 2 gm. benzoic acid) are given, all of it is normally eliminated as hippuric acid, but that in nephritic and cardio-renal patients the synthesis is never complete (53 to 95 per cent. of the theory). Delayed excretion of hippuric acid by the diseased kidney has also been noted by Snapper and Grünbaum[2] and by Bryan.[3]

d-Alanin ($CH_3.CHNH_2.COOH$).—*All three carbon atoms are able to enter into the formation of glucose. Found in all true proteins. In zein as much as* 13.4 *per cent., in muscle protein about* 8 *per cent. is present; in gelatin* 9 *per cent.; in gliadin* 2 *per cent.*

Neuberg[4] found glycogen in the liver and lactic acid in the urine of a normal rabbit following the ingestion of alanin. The amino-acid had been converted into lactic acid with the elimination of ammonia. Ringer and Lusk[5] gave 20 grams of i-alanin to a phlorhizinized dog and witnessed its complete elimination in the form of urinary glucose. Dakin[6] obtained the same result after administering l-alanin.

Mandel and Lusk[7] showed that d-lactic acid was completely converted into glucose in the diabetic organism and as much as 70 per cent. of the d-l-lactic acid could be transformed.

Dakin has emphasized the fact that these experiments demonstrate that the loss of asymmetry of the central carbon atom of l-alanin or of l-lactic acid is essential for the formation of d-glucose. Such a loss of asymmetry would occur in the case of alanin if it were converted into pyruvic acid by oxidative deamination.



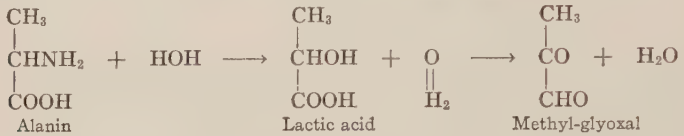
Alanin — Pyruvic acid

This is a possible pathway, for pyruvic acid is convertible into glucose when administered to the glycosuric organism.[8] Levene[9]

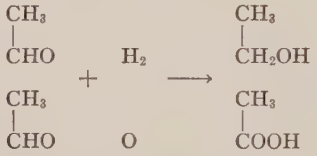
[1] Morgulis, S., Pratt, G. P., and Jahr, H. M.: Arch. Int. Med., 1923, **31**, 116.
[2] Snapper, J., and Grünbaum, A.: Klin. Wochenschr., 1924, **3**, 101.
[3] Bryan, A. W.: J. Clin. Invest., 1925–26, **2**, 1.
[4] Neuberg, C., and Langstein, L.: Arch. f. Physiol., 1903, Suppl. p. 514.
[5] Ringer, A. I., and Lusk, G.: Z. physiol. Chem., 1910, **66**, 106.
[6] Dakin, H. D., and Dudley, H. W.: J. Biol. Chem., 1914, **17**, 451.
[7] Mandel, A. R., and Lusk, G.: Am. J. Physiol., 1906, **16**, 129.
[8] Ringer, A. I.: J. Biol. Chem., 1913, **15**, 145; 1914, **17**, 281; Dakin, H. D., and Janney, N. W.: *Ibid.*, 1913, **15**, 177; Cremer, M.: Berliner klin. Wchnschr., 1913, **50**, 1457.
[9] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1914, **17**, 443.

finds that aseptic preparations of leucocytes or kidney tissue effect no chemical change of pyruvic acid, this being contrary to the action of yeast cells which converts it into acetaldehyd with cleavage of CO_2 (see p. 327).

If alanin be convertible into lactic acid by hydrolysis, the asymmetry of the central carbon atom could be eliminated by a *reversed internal Cannizzaro reaction*, as follows:

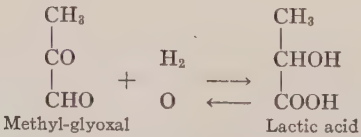


The *Cannizzaro reaction* involves the conversion of two molecules of aldehyd into one of acid and one of alcohol through the mediation of water. Thus, Battelli and Stern[1] observed that tissue converted acetaldehyd into alcohol and acetic acid.



The enzyme accomplishing this reaction is called "aldehyd mutase" by Parnas.[2]

The *internal Cannizzaro reaction* deals with the oxidation of aldehyd and reduction of the keto radicles in the same compound. This may be illustrated by the conversion of methyl-glyoxal into lactic acid, which Dakin[3] and Neuberg[4] have shown is rapidly effected by tissue *in vitro*. Dakin calls the enzymes accomplishing these reactions "glyoxylases," while Neuberg prefers the name "keto-aldehyd mutase."

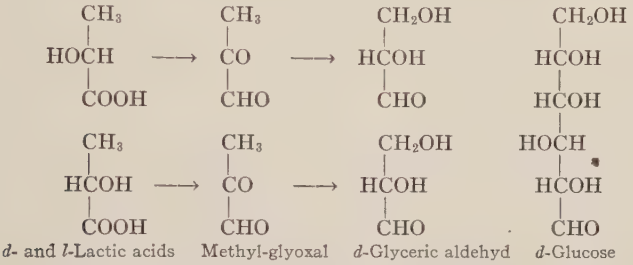


The reversed internal Cannizzaro reaction accomplishes the conversion of lactic acid into methyl-glyoxal.

[1] Battelli, F., and Stern, L.: Compt. rend. soc. biol., 1910, **68**, 742.
[2] Parnas, J.: Biochem. Z., 1910, **28**, 274.
[3] Dakin, H. D., and Dudley, H. W.: J. Biol. Chem., 1913, **14**, 155, 423.
[4] Neuberg, C.: Biochem. Z., 1913, **49**, 502.

Dakin[1] gave 9 grams of methyl-glyoxal to a phlorhizinized dog and obtained 7 grams of extra sugar in the urine, while 12 grams of l-lactic acid yielded 9 grams of extra glucose.

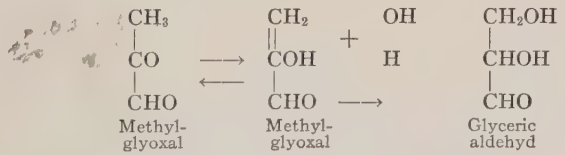
These experiments enabled Dakin to picture the transformation of a d-l-alanin through d-l-lactic acid into d-glucose, as follows:



Neuberg[2] reached essentially similar conclusions.

Ringer and Lusk[3] showed that glyceric acid was convertible into glucose in the phlorhizinized dog, and the same was shown for glyceric aldehyd by Sansum and Woodyatt.[4]

It has been difficult to find a chemical analogy to the transformation of the CH_3 group of methyl-glyoxal into $-CH_2OH$ in glycerin aldehyd. It is certain that the CH_3 groups in lactic acid and alcohol both arise in biochemical reactions from glucose, yet the manner of origin is unknown.[5] Dakin (oral statement to the writer) presents a solution of the problem dependent upon the interconversion of tautomeric forms of methyl-glyoxal:



Since fructose[6] and many other hexose sugars yield methyl-glyoxal with readiness *in vitro*, there is much likelihood that this is the intermediary substance produced when fructose and galactose,

[1] Dakin, H. D., and Dudley, H. W.: J. Biol. Chem., 1913, **15**, 127.
[2] Neuberg, C.: Biochem. Z., 1913, **51**, 484.
[3] Ringer, A. I., and Lusk, G.: Z. physiol. Chem., 1910, **66**, 106.
[4] Sansum, W. D., and Woodyatt, R. T.: J. Biol. Chem., 1915, **21**, 1.
[5] Neuberg, C., and Rewald, B.: Biochem. Z., 1914, **67**, 127.
[6] Wohl, A.: *Ibid.*, 1907, **5**, 45.

for example, are converted into glucose by the diabetic or into glycogen (which yields glucose) in the normal organism. The above described transformation, first postulated by Nef,[1] is, therefore, of fundamental biologic significance not only in the metabolism of alanin but also as regards that of carbohydrate.

It may be added that it is stated that alanin may be formed synthetically from pyruvic acid,[2] when this substance is perfused through the liver, or from glycogen[3] when an ammonium salt is perfused through a liver rich in glycogen. The synthetic production of amino-acids has already been discussed (see p. 219).

It appears from this analysis that the amino-acid alanin yields on deamination an acid which may readily be converted into glucose or into methyl-glyoxal, a direct cleavage product of glucose, and which, therefore, may behave like glucose in the organism. Consideration of the oxidation of glucose will be found in Chapter XIV.

Valin ($(CH_3)_2$:CH.CHNH$_2$.COOH).—*Present in small amounts in most proteins. Fate obscure.*

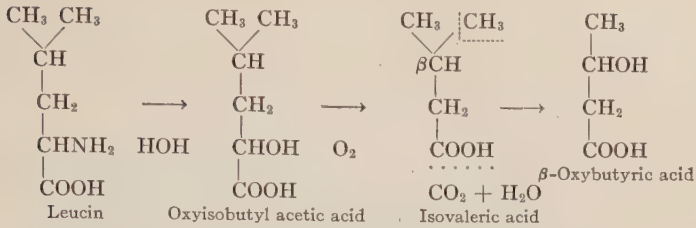
By the method of liver perfusion, Embden, Salomon, and Schmidt[4] could find no aceton bodies arising from valin.

Dakin[5] gave valin to a phlorhizinized dog, but could find no clear evidence of glucose or β-oxybutyric acid formation from it. Its oxy-acid, α-oxy-isovalerianic acid, also yielded little or no sugar.

Leucin ($(CH_3)_2$:CH.CH$_2$.CHNH$_2$COOH).—*Present in all proteins. Convertible into β-oxybutyric acid.*

Leucin when given to a phlorhizinized dog produces little or no glucose.[6] When added to a perfusing fluid and passed through a surviving liver leucin yields aceton bodies in large amounts.[7] Baer and Blum[8] found a greatly increased output of β-oxybutyric acid after giving 33.7 grams of leucin to a diabetic patient. The chemical reaction undoubtedly follows the known laws of oxidation on the α-amino group of the amino-acids of β-oxidation and cleavage of a methyl radicle whose further fate is unknown. These reactions may thus be presented:

[1] Nef, J. U.: Liebig's Ann., d. Chem. u. Pharm. 1904, **335**, 247.
[2] Embden, G., and Schmitz, E.: Biochem. Z., 1911–12, **38**, 393.
[3] Fellner, H.: *Ibid.*, 1911–12, **38**, 414.
[4] Embden, G., Salomon, H., and Schmidt, F.: Hofmeister's Beitr. chem. Physiol. u. Path., 1906, **8**, 129.
[5] Dakin, H. D.: J. Biol. Chem., 1913, **14**, 321.
[6] Halsey, J. T.: Am. J. Physiol., 1903–04, **10**, 229; Dakin, H. D.: *Loc. cit.*
[7] Embden, G., Salomon, H., and Schmidt, F.: *Loc. cit.*
[8] Baer, J., and Blum, L.: Arch. exper. Path. u. Pharm., 1906, **55**, 89.



The end-product of the metabolism of leucin is, therefore, the same as the end-product of ordinary fat metabolism.

l-Phenylalanin, $C_6H_5.CH_2.CHNH_2COOH$, and **l-Tyrosin,** $HOC_6H_4.CH_2.CHNH_2COOH$.—*Yield β-oxybutyric acid, and in alcaptonuria homogentisic acid. Present in all proteins, except that tyrosin is absent in gelatin.*

The metabolism of these substances has already been considered in some detail (see p. 213). Embden and Baldes[1] state that when phenylalanin is added to the perfusing fluid passing through the liver it may be converted into tyrosin. Even though phenylalanin does not always yield tyrosin in the organism, yet it is believed that it may be converted into p-oxyphenylpyruvic acid, which is the first oxidation product of tyrosin.

In the phenomenon called *alcaptonuria* (see p. 213), tyrosin and phenylalanin are believed to be oxidized only as far as *homogentisic acid*, in which form they appear in the urine.

It is interesting that pulps of liver, kidney and spleen, and liver perfusion, in the dog, always convert oxyphenylpyruvic acid into l-oxy-phenyl lactic acid.[2]

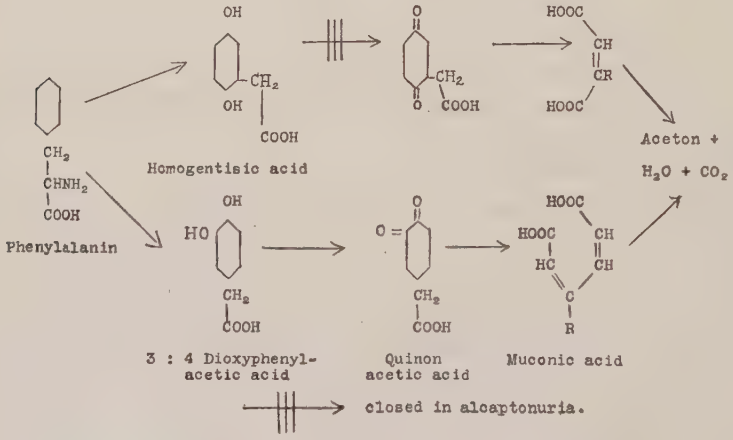
The disease in man was first described by Bödeker[3] in 1859. The bladder urine, which appeared normal on voiding, turned dark brown or black on exposure to the air. Wolkow and Baumann[4] were the first to show that the abnormal constituent was homogentisic acid. People afflicted with this abnormality enjoy perfectly good health. J. H. Lewis[5] reports that between 50 and 60 cases have been described in men and that he has discovered the disease in a rabbit which voided a urine which became inky black on exposure to the air and gave reactions for homogentisic acid.

[1] Embden, G., and Baldes, K.: Biochem. Z., 1913, **55,** 301.
[2] Mori, Y., and Kanai, T.: Z. f. Physiol. Chem., 1922, **122,** 206.
[3] Bödeker: Z. f. rationelle Med., 1859, **7,** 130.
[4] Wolkow, M., and Baumann, E.: Z. physiol. Chem., 1891, **15,** 228.
[5] Lewis, J. H.: J. Biol. Chem., 1926, **70,** 659.

Falta[1] reports that if phenylalanin or tyrosin be administered in alcaptonuria each is completely converted into homogentisic acid and so eliminated. In alcaptonuria the ratio between homogentisic acid and nitrogen elimination in the urine is quite constant, being 45:100 or 50:100,[2] and the distribution of the various other nitrogenous compounds in the urine remains normal.

Neubauer and Falta[3] emphasized the idea that homogentisic acid is always formed in normal metabolism but in this rare disease cannot be oxidized. The power to split the benzol ring is absent.

However, Dakin[4] has administered to alcaptonurics paramethylphenylalanin, $CH_3.C_6H_4.CH_2CHNH_2COOH$, and paramethoxyphenylalanin, $CH_3O.C_6H_4.CH_2CHNH_2COOH$, substances which cannot undergo the quinoid transformation (see p. 213), and has found that these are oxidized in the organism. He, therefore, concludes that the formation of homogentisic acid in metabolism is always pathologic, and that the benzol ring can be broken even in alcaptonuria without a quinoid intermediate. Fromherz and Hermanns[5] believe that the aromatic amino-acids normally follow a dual path to destruction and that one of these is closed in alcaptonuria, whereas the other remains open. They present this picture of the process:



[1] Falta, W.: Biochem. Centralbl., 1904–05, **3,** 175.

[2] Langstein, L. and Meyer, E.: Deut. Arch. klin. Med., 1903, **78,** 161; Schumm, O.: Münchener med. Wchnschr., 1904, **51,** 1599; Garrod, A. E., and Hele, T. S.: J. Physiol. 1905, **33,** 205; Ravold, A., and Warren, W. H.: J. Biol. Chem., 1909–10, **7,** 465.

[3] Neubauer, O., and Falta, W.: Z. physiol. Chem., 1904, **42,** 81.

[4] Dakin, H. D.: J. Biol. Chem., 1911, **9,** 151.

[5] Fromherz, K., and Hermanns, L.: Z. physiol. Chem., 1914, **91,** 194.

It will be recalled that muconic acid has been considered as representing the opening door of the benzol ring, ever since Jaffé[1] gave benzol to a rabbit and found muconic acid in the urine.

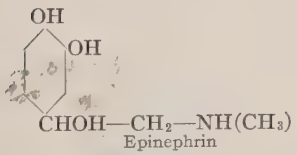
Phenylalanin, tyrosin, homogentisic acid,[2] and muconic acid[3] all yield aceton bodies when perfused through a surviving liver.

The reaction involving the production of β-oxybutyric acid cannot yet be written, though two of its four carbon atoms are probably derived from the phenyl ring and two from the side chain.[4]

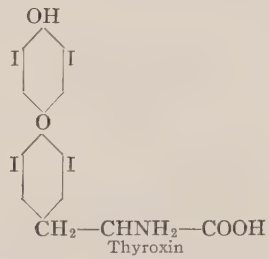
Tyrosin yields no sugar in the phlorhizinized dog,[5] nor does phenylalanin.[6]

When the ammonium salts of the keto-acids corresponding to phenylalanin and tyrosin are perfused through a surviving liver there may be a synthetic production of the two last-named substances.[7] The reaction of deamination is, therefore, reversible in these cases.

One should mark the chemical analogy between tyrosin, epinephrin, and thyroxin. Epinephrin was first obtained as a benzoyl derivative by Abel.[8] Thyroxin was first obtained in pure form by Kendall,[9] who showed that it contained 65 per cent. of iodin. Harington[10] discovered the formula for thyroxin, and subsequently its synthetic production was accomplished by Harington and Barger.[11] The synthetic compound has the same physiological effectiveness as Kendall's natural thyroxin.



Epinephrin



Thyroxin

This story would not be complete without adding Harington's footnote (1927) regarding an exceptionally noteworthy record of human behavior:

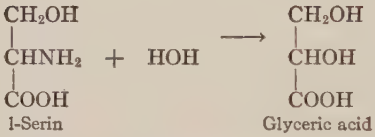
[1] Jaffé, M.: Z. physiol. Chem., 1909, **62**, 58.
[2] Embden, G., Salomon, H., and Schmidt, F.: *Loc. cit.*
[3] Hensel, M., and Riesser, R.: Z. physiol. Chem., 1913, **88**, 38.
[4] Wakeman, A. J., and Dakin, H. D.: J. Biol. Chem., 1911, **9**, 139.
[5] Ringer, A. I., and Lusk, G.: *Loc. cit.*; confirmed by Dakin.
[6] Dakin, H. D.: J. Biol. Chem., 1913, **14**, 321.
[7] Embden, G., and Schmitz, E.: Biochem. Z., 1910, **29**, 423.
[8] Abel, J. J.: Johns Hopkins Hosp. Bull., 1898, **9**, 215.
[9] Kendall, E. C.: J. Biol. Chem., 1914, **19**, 251.
[10] Harington, C. R.: Biochem. J., 1926, **20**, 300.
[11] Harington, C. R., and Barger, G.: *Ibid.*, 1927, **21**, 169.

"I have since learned that Dr. H. D. Dakin had come simultaneously to substantially the same conclusions as myself regarding the constitution of thyroxin . . . On hearing from Prof. Barger that I had communicated a paper on the subject to the *Biochemical Journal*, Dr. Dakin withdrew his paper, which was at that time in the hands of the Editor of the *Journal of Biological Chemistry*, from publication."

It is noteworthy that Abderhalden[1] in 1924 found that 3–5 diiodotyrosin, in concentration of 1.5 mg. per 100 c.c. of water, promoted the growth and metamorphosis of tadpoles after the same manner that Gudernatsch[2] found thyroxin affected them.

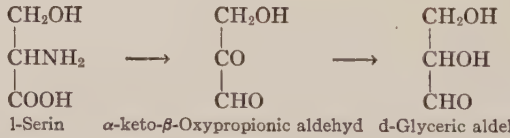
l-Serin, $CH_2OH.CHNH_2COOH$.—*Detected in small quantities in many proteins. Three carbon atoms are able to enter into the formation of glucose.*

Dakin[3] showed that the ingestion of 11.9 grams of serin by a phlorhizinized dog resulted in the excretion of 11 grams of extra glucose in the urine. One might picture the conversion of serin into glyceric acid which Ringer and Lusk (p. 233) showed is transformed into glucose:



l-Serin Glyceric acid

But in order to remove the asymmetry of the central carbon atom it seems more probable that a keto-body is an intermediary oxidative product. The transformation might take the following form:



l-Serin α-keto-β-Oxypropionic aldehyd d-Glyceric aldehyd

Its possible production from alanin has already been discussed (p. 216).

Cystin, $\begin{matrix} S—CH_2.CHNH_2COOH \\ | \\ S—CH_2.CHNH_2COOH \end{matrix}$.—*Present in most proteins. Six carbon atoms probably may enter into the formation of glucose.* The relation of cystin to the oxidation-reduction system of glutathion

[1] Abderhalden, E.: Pflüger's Arch. gesam. Physiol., 1924, **206,** 467.
[2] Gudernatsch, J. F.: Zentralbl. f. Physiol., 1912, **26,** 323.
[3] Dakin, H. D.: *Loc. cit.*

has already been discussed. Cystin is the principal sulphur-containing constituent of protein (see p. 180).

In a rare disease called cystinuria cystin appears dissolved in the urine, or it may take the form of stone or of sediment. If cystin be administered to a normal person it is oxidized, and does not alter the normal relation between oxidized and unoxidized sulphur in the urine.[1] If cystin be given to a patient with cystinuria it is oxidized as in the normal person.[2] The disturbance, therefore, is not complete. But when protein is given in increased measure the cystin elimination is largely increased in the cystinuric patient.[3] The increase in neutral sulphur found in the urine is at the expense of the alkaline sulphate usually found there. It would seem therefore that the sulphur of ingested protein is not absorbed in the form of cystin free and uncombined,[4] but rather as a polypeptid, possibly glutathion.

In cystinuria the metabolism of the other amino-acids is entirely normal.

In normal metabolism cystin is probably first broken up into two molecules of cystein, for on giving brombenzol *mercapturic acid* appears in the urine. This acid is a compound of cystein, brombenzol, and acetic acid. The reaction, as shown by Friedmann,[5] takes place as follows:

$$\begin{array}{l} CH_2SH \\ | \\ CHNH_2 \\ | \\ COOH \end{array} + C_6H_5Br + CH_3COOH = \begin{array}{l} CH_2S.C_6H_4.Br \\ | \\ CHNH.CO.CH_3 \\ | \\ COOH \end{array} + H_2$$

Cystein — Brombenzol — Acetic acid — Brombenzol mercapturic acid

This affords an example of *acetylation* not uncommon in the organism[6] (see p. 220).

Marriott and Wolf[7] further investigated this condition of artificially induced cystinuria, and were able to increase the unoxidized sulphur (cystein-S) in the urine fourfold by this means, and nearly

[1] Blum, L.: Hofmeister's Beitr. chem. Physiol. 1904, **5**, 1.
[2] Williams, H. B., and Wolf, C. G. L.: J. Biol. Chem., 1909, **6**, 337.
[3] Alsberg, C., and Folin, O.: Am. J. Physiol., 1905, **14**, 54.
[4] Looney, J. M., Berglund, H., and Graves, R. C.: J. Biol. Chem., 1923, **57**, 515.
[5] Friedmann, E.: Hofmeister's Beitr. chem. Physiol. 1904, **4**, 486.
[6] Consult von Fürth, O.: "Probleme der physiologischen und pathologischen Chemie," Leipzig, 1913, **2**, p. 465.
[7] Marriott, W. M., and Wolf, C. G. L.: Am. Med., 1905, **9**, 1026. See also Zeller, H., and Straczewski, H.: Arch. f. Physiol., 1914, p. 585.

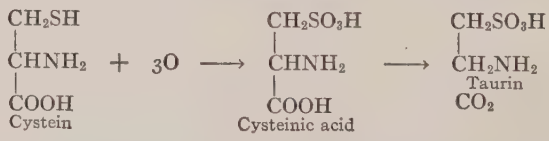
to remove all the oxidized sulphur. The sulphur was, therefore, not oxidized to sulphate as in the normal state.

Karl Thomas[1] made the striking discovery that when brombenzol was given to dogs, the protein metabolism of which had been reduced to the "wear and tear" level through the ingestion of large quantities of carbohydrate, no production of mercapturic acid occurred. This experiment was confirmed by Sherwin and his pupils.[2] They also administered to dogs prepared as above the following substances: sodium sulphate, potassium thiocyanate, calcium sulphid, taurin, and ethyl amino mercaptan, without causing any production of mercapturic acid. Only when cystin itself was given did mercapturic acid appear in the urine. The body therefore appears to have no synthetic power to form cystin such as it has to form glycin.

The same authors[3] have investigated the method of the formation of urinary sulphates. A hog was given starch alone until the urinary nitrogen was reduced to 1.1 gm. daily. The addition of 3 gm. of cystin to the diet caused a rise in urinary nitrogen to 2.4 gm., almost no rise in neutral or in ethereal sulphur, whereas the inorganic sulphate rose from 0.06 gm. to 0.4 gm. When 0.8 gm. phenol alone was administered to the starch fed hog the ethereal sulphates rose in the urine; when given with 4 gm. cystin the increase was even greater; but when phenol was given with sodium sulphate there was no increase in ethereal sulphate beyond that which phenol alone would have produced. The detoxication of phenol therefore is due to a prior union with cystin or one of its decomposition products with the resulting formation of ethereal sulphate. Inorganic sulphates, once formed from the oxidation of cystin, are powerless to effect this synthesis.

However, Rhode[4] reports that sodium sulphite (Na_2SO_3) unites with phenol in the rabbit to produce ethereal sulphate.

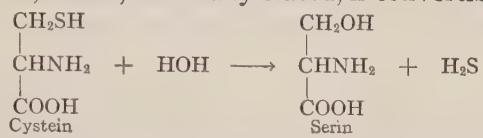
That cystein is the mother substance of the taurin of the bile Friedmann[5] illustrates in accordance with the following formula:



[1] Thomas, K., and Straczewski, H.: Arch. f. Physiol., 1919, p. 249.
[2] Muldoon, J. A., Shiple, G. J., and Sherwin, C. P.: J. Biol. Chem., 1924, **59**, 675.
[3] Shiple, G. J., Muldoon, J. A., and Sherwin, C. P.: *Ibid.*, 1924, **60**, 59.
[4] Rhode, H.: Z. physiol. Chem., 1923, **124**, 15.
[5] Friedmann, E.: Hofmeister's Beitr. chem. Physiol., 1903, **3**, 1.

Neither taurin[1] nor cysteinic acid[2] can replace cystin in the dietary as substitutes for this necessary component.[3]

Taurin, however, is not the only pathway of cystein destruction, for Dakin[4] gave a phlorhizinized dog 15.7 grams of cystein, which theoretically is convertible into at most 11.6 grams of glucose, and found 12.2 grams of extra glucose in the urine. This transformation would be conceivable through hydrolysis and the conversion of cystein into serin, which, as already stated, is convertible into glucose.



Dakin made note of the fact that the sulphur excretion under the conditions of his experiments was in the form of sulphate and was relatively very slow. This is contrary to the usual behavior of the sulphur contained in cystein (see p. 202).

It is evident that cystein metabolism has the choice of at least two different pathways in the organism.

H. B. Lewis[5] can hardly believe that the cleavage of hydrogen sulphid and its oxidation to sulphate can be regarded as the main reaction in the oxidation of sulphur under normal conditions. He says the point of attack is not known with certainty. He[6] finds that when the NH_2 group is combined the sulphur is not attacked. Thus phenyluramino-cystin and dibenzoyl cystin administered subcutaneously are not attacked but are eliminated unchanged in the urine. He believes therefore that there is a close relation between the oxidation of the cystein sulphur and the process of deamination. The conjugation of the amino group of cystin with the carboxyl group of glutamic acid is the cause which prevents the oxidation of the sulphur of glutathion (see p. 180) to sulphuric acid.

Curtis and Newburgh[7] state that cystin, when given to rats in considerable quantity, is toxic, resulting in kidney and liver necrosis and death of the animal.

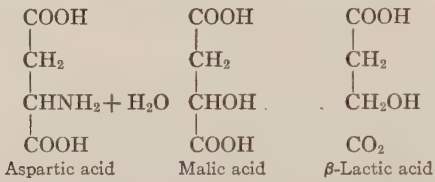
Inorganic sulphates play no rôle in nutrition,[8] being only end products of oxidation.

[1] Beard, H. H.: Am. J. Physiol., 1925–26, **75,** 658.
[2] Lewis, G. T., and Lewis, H. B.: J. Biol. Chem., 1926, **69,** 589.
[3] Rose, W. C., and Huddlestun, B. T.: *Ibid.*, 1926, **69,** 599.
[4] Dakin, H. D.: *Loc. cit.*
[5] Lewis, H. B.: Physiol. Rev., 1924, **4,** 408.
[6] Lewis, H. B., Updegraff, H., and McGinty, D. A.: J. Biol. Chem., 1924, **59,** 59.
[7] Curtis, A. C., and Newburgh, L. H.: Arch. Int. Med., 1927, **39,** 817, 828.
[8] Daniels, A. L., and Rich, J. K.: J. Biol. Chem., 1918, **36,** 27.

Aspartic acid, $HOOC.CH_2.CHNH_2.COOH$.—*Present in most proteins. Three carbon atoms enter into the formation of glucose.*

Chibnall[1] found that the leaves of the bean plant contain 35 to 40 per cent. of their nitrogen in the form of asparagin, the amid of aspartic acid. He believes it to be the chief agent whereby nitrogen suitable for the synthesis of protein is conveyed from one part of the plant to another.

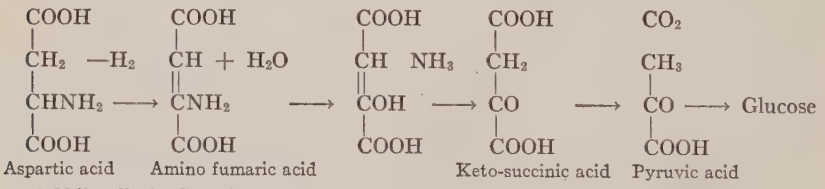
Aspartic acid was given to phlorhizinized dogs by Ringer and Lusk[2] and the equivalent of three carbon atoms was recovered as glucose in the urine. This has been confirmed in Cremer's laboratory by Hering,[3] who administered asparagin and also by Langer[4] who gave aspartic acid. The possible pathways of this transformation are several. Ringer and Lusk gave the following course:



Later Ringer[5] found that malic acid was in large measure convertible into glucose.

This conception of intermediary reaction is supported by the finding of Ackermann[6] that digestion of aspartic acid with putrid pancreas produces β-alanin, $H_2NCH_2.CH_2.COOH$.

Dakin[7] considers that alanin or lactic acid are the primary cleavage products of aspartic acid metabolism, and this is attested by the researches of Mayer[8] in Neuberg's laboratory, who finds that tissue pulp of liver and muscle convert keto-succinic acid into pyruvic acid. The modernized reaction would be as follows:

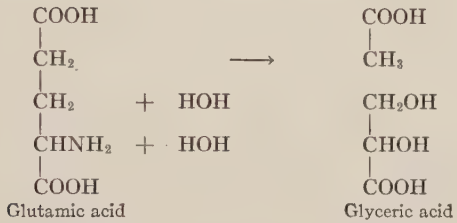


[1] Chibnall, A. C.: Biochem. J., 1924, **18,** 395.
[2] Ringer, A. I., and Lusk, G.: *Loc. cit.*
[3] Hering, F.: Cremer's Beitr. z. Physiol., 1914, **1,** 1.
[4] Langer, W.: *Ibid.*, 1922-24, **2,** 47.
[5] Ringer, A. I., Frankel, E. M., and Jonas, L.: J. Biol. Chem., 1913, **14,** 539.
[6] Ackermann, D.: Z. f. Biol., 1911, **56,** 87.
[7] Dakin, H. D.: *Loc. cit.*
[8] Mayer, P.: Biochem. Z., 1914, **62,** 462.

One, or perhaps both, of these pathways are open in the organism for the metabolism of aspartic acid and for synthesis of glucose from it should conditions favor.

Glutamic Acid, $HOOC.CH_2.CH_2.CHNH_2.COOH$.—*Present in all proteins, frequently largest constituent amino-acid in the molecule, as in gliadin of wheat* (44 *per cent.*) *and in muscle* (22 *per cent.*). *Three carbon atoms enter into the formation of glucose.*

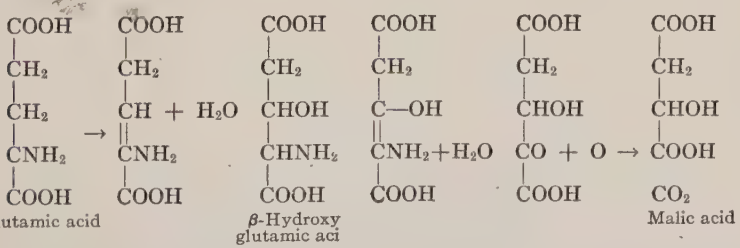
This was the first amino-acid whose power to form glucose was measured.[1] Ringer and Lusk held that this power to form glucose was through β-oxidation of the central carbon atom, as follows:



Since glyceric acid forms glucose, this pathway would be a natural one. Warkalla[2] confirms the synthesis of three carbon groups of glutamic acid into glucose.

Dakin[3] has isolated β-**hydroxyglutamic acid** from casein, gliadin, and glutenin and has also synthesized the substance. Given to a phlorhizinized dog, between 50 and 55 per cent. of it pass into extra glucose in the urine. If three carbon atoms had been converted into glucose, then 55 per cent. of the molecule would appear as glucose.

It is of course quite speculative to define exactly the transformations which take place, but the following is suggestive of one of the possibilities:



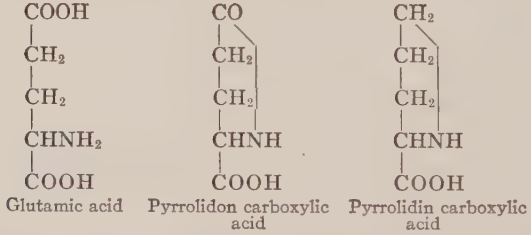
Malic acid, through decarboxylation, is convertible into lactic acid and this into glucose.

[1] Lusk, G.: Am. J. Physiol., 1908, **22,** 174.
[2] Warkalla, B.: Cremer's Beitr. z. Physiol., 1914, **1,** 91.
[3] Dakin, H. D.: Biochem. J., 1919, **13,** 398.

F. Ehrlich[1] showed that fermenting yeast converted glutamic acid into succinic acid, $HOOC.CH_2.CH_2.COOH$, and Neuberg[2] finds that keto-glutaric acid, $HOOC.CH_2.CH_2.CO.COOH$, yields the same product under similar conditions. This indicates keto-glutaric acid as a probable intermediary product. Since Ringer[3] has shown that succinic acid is convertible into glucose, this appears to be a possible pathway of the decomposition of glutamic acid.

An interesting phenomenon which occurs in man was discovered by Thierfelder and Sherwin,[4] who showed that, although the ingestion of sodium benzoate by a human being occasions the elimination of hippuric acid in the urine, the administration of phenylacetic acid results in its conjugation, not with glycin, but with glutamin. After giving 15 gm. of phenylacetic acid to a man partaking of a diet free from protein, 14.75 gm. of phenyl-acetyl-glutamin containing 7.5 gm. glutamin were recovered in the urine by Sherwin[5] and his pupils. Although the total urinary N was not determined, Sherwin concludes that glutamic acid, like glycin, can be synthesized by the human being for detoxicating purposes.

According to Abderhalden,[6] glutamic acid may be condensed into pyrrolidon carboxylic acid. The conversion of this into prolin or pyrrolidin carboxylic acid has not yet been achieved.



Glutamic acid — Pyrrolidon carboxylic acid — Pyrrolidin carboxylic acid

Pyrrolidin carboxylic acid made in some such manner may become the mother substance used in the construction of hemoglobin in the animal or of chlorophyll in the plant.

Lysin, $NH_2.CH_2.CH_2.CH_2.CH_2.CHNH_2.COOH$.—*Present in proteins of animal origin. Absent in zein and present in very small amount in such a vegetable protein as gliadin. It is the only amino-acid with a straight chain which does not form glucose.*

[1] Ehrlich, F.: Biochem. Z., 1909, **18**, 391.
[2] Neuberg, C., and Ringer, M.: *Ibid.*, 1915, **71**, 226.
[3] Ringer, A. I., Frankel, E. M., and Jonas, L.: J. Biol. Chem., 1913, **14**, 539.
[4] Thierfelder, H., and Sherwin, C. P.: Ber. chem. Ges., 1914, **47**, 2630.
[5] Sherwin, C. P., Wolf, M., and Wolf, W.: J. Biol. Chem., 1919, **37**, 113.
[6] Abderhalden, E., and Kautzsch, K.: Z. physiol. Chem., 1910, **68**, 487.

Hart, Nelson and Pitz[1] do not believe that the body as a whole or the lactic glands can synthetically produce lysin.

Dakin[2] gave lysin to a phlorhizinized dog, but found neither extra sugar nor an increase in the β-oxybutyric acid excretion in the urine. This is explained by Ringer[3] on the ground that lysin may be converted into glutaric acid, $HOOC.C_3H_6.COOH$, which does not form glucose when administered in phlorhizin glycosuria.[4] The small increase in β-oxybutyric acid elimination noted by Ringer in this experiment does not necessarily indicate that this substance is an intermediary metabolism product.

The oxidation to COOH of the ε-C, to which an NH_2 group is attached, followed by β-oxidation, would yield aspartic acid, provided the NH_2 in the β-position remained untouched. Such a course of metabolism would cause lysin to yield glucose in abundance and is therefore excluded.

Bacteria in intestinal putrefaction convert lysin into cadaverin, $NH_2—C_5H_{10}—NH_2$, through simple CO_2 cleavage. In severe cases of cystinuria the diamines cadaverin and putrescin (see p. 246) appear in the urine and this constitutes diaminuria.[5]

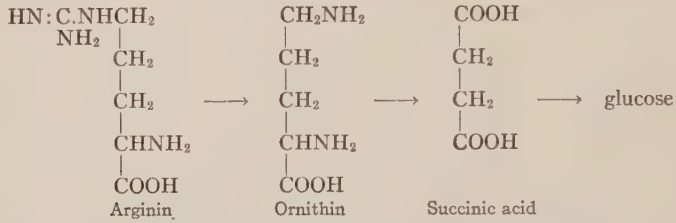
Arginin, $NH_2.CNHNH.CH_2CH_2CH_2.CHNH_2.COOH$.—*Present in most proteins. Probably three carbon atoms form glucose.*

Kossel and Dakin[6] found that liver but not muscle contained an enzyme capable of splitting d-arginin into urea and ornithin, the only reaction by which urea is obtained as a simple cleavage product of an amino-acid. Arginase is found only in the liver, and carcinoma of the liver and phosphorus poisoning do not affect its activity there.[7]

In mammals arginin is completely transformed into urea and ornithin by the liver, and the latter is largely transformed there, as perfusion experiments show.[8] However the dipeptid of arginin, arginyl-arginin is not split by the liver but passes through it unchanged.[9] Dakin[10] gave both arginin and ornithin to a phlorhizinized dog, and witnessed a sufficient elimination of extra glucose to

[1] Hart, E. B., Nelson, V. E., and Pitz, W.: J. Biol. Chem., 1918, **36,** 291.
[2] Dakin, H. D.: *Loc. cit.*
[3] Ringer, A. I., Frankel, E. M., and Jonas, L.: *Loc. cit.*
[4] Ringer, A. I.: J. Biol. Chem., 1912, **12,** 223.
[5] Literature, v. Fürth, O.: "Probleme der physiologischen und pathologischen Chemie," 1913, Leipzig, p. 117.
[6] Kossel, A., and Dakin, H. D.: Z. physiol. Chem., 1904, **41,** 321; 1904, **42,** 183.
[7] Fuchs, B.: *Ibid.*, 1921, **114,** 101.
[8] Felix, K., and Tomita, M.: *Ibid.*, 1923, **128,** 40.
[9] Felix, K., and Morinaka, K.: *Ibid.*, 1924, **132,** 152.
[10] Dakin, H. D.: *Loc. cit.*

account for three of the carbon atoms in these substances. Since three carbon atoms of succinic acid enter into the formation of glucose, and succinic acid appears to be a possible product of the metabolism of ornithin, one may assume that this might represent the pathway into sugar. These formulæ may thus be portrayed:



Another possible pathway would be the oxidation of the δ-C atom of ornithin to COOH, with the production of glutamic acid, which would then break up with sugar formation (see p. 243).

The liver of the fowl contains no arginase.[1] When benzoic acid is administered to fowls it unites with ornithin in the body and is eliminated in the form of ornithuric acid, which is α-δ-di benzoyl-ornithin.[2] Only arginin ingestion will increase the quantity of ornithuric acid eliminated, and histidin has no effect on the output; hence histidin cannot be readily converted into arginin.[3]

Bacteria in the intestine may convert ornithin into *putrescin*, $NH_2—C_4H_8—NH_2$, through the cleavage of CO_2 (see p. 245).

Arginin is the only amino-acid containing the guanidin nucleus, which is also found in creatin. However, attempts to associate the origin of creatin from arginin have proved fruitless. Jaffé[4] gave nitrate of arginin subcutaneously to a rabbit, but found no change in the amount of creatin in the urine or muscle. According to the known laws of oxidation of amino-acids, guanidin acetic acid, $NH_2.CNH.NH.CH_2.COOH$, might readily be an oxidation product of arginin. When Jaffé gave this substance to a rabbit he found that a methyl group was added and it was in part eliminated in the urine as creatin, $NH_2.CNH.NCH_3.CH_2.COOH$. The proof of the origin of guanidin acetic acid in the organism is, however, lacking. Arginase does not effect the cleavage of creatin or guanidin acetic acid[5] (see also p. 252).

[1] Edelbacher, S.: Z. physiol. Chem., 1917, **100**, 111.
[2] Jaffé, M.: Ber. chem. Ges., 1877, **10**, 1925; 1878, **11**, 406.
[3] Crowdle, J. H., and Sherwin, C. P.: J. Biol. Chem., 1923, **55**, 365.
[4] Jaffé, M.: Z. physiol. Chem., 1906, **48**, 430.
[5] Dakin, H. D.: J. Biol. Chem., 1907, **3**, 435.

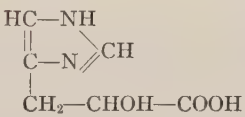
Karl Thomas has been greatly interested in the origin of creatin but has not found the connecting link between the metabolism of arginin and the formation of creatin. Thomas, Kapfhammer and Flaschenträger[1] find that δ-methylarginin is not the mother substance of creatin.

Histidin $N{:}CH.NH.CH{:}C.CH_2.CHNH_2.COOH$.—*Present in most proteins. Does not produce glucose, and there is no clear evidence that it produces β-oxybutyric acid.*

When histidin is given to dogs it is oxidized and urea formed from it appears in the urine.[2] When it is given to phlorhizinized dogs Dakin[3] finds no clear-cut evidence that it is converted either into glucose or β-oxybutyric acid.

Histidin gives Ehrlich's diazo-reaction, and is probably the chromogen within urochrom.[4]

It has been stated that histidin and arginin are "interchangeable" amino-acids in a dietary.[5] Rose and Cox,[6] however, find that the absence of histidin from the diet of rats produces marked loss in weight and a general decline irrespective of the amount of arginin given. When imidazol lactic acid was added to the



histidin-free diet of a rat, growth was resumed. Harrow and Sherwin[7] confirm this result and state that imidazol pyruvic acid to a lesser extent is able to replace histidin in the dietary, but that imidazol acrylic acid is without influence. These authors query whether imidazol lactic and pyruvic acids undergo reversible reactions which would lead to the production of histidin.

Ackroyd and Hopkins called attention to the chemical relation between histidin and the purins. Stewart[8] points out that when a diet free from arginin and histidin is given, the excretion of allantoin

[1] Thomas, K., Kapfhammer, J., and Flaschenträger, B.: Z. physiol. Chem., 1923, **124,** 75.

[2] Abderhalden, E., and Einbeck, H.: *Ibid.*, 1909, **62,** 322; 1910, **68,** 395.

[3] Dakin, H. D.: J. Biol. Chem., 1913, **14,** 328.

[4] von Fürth, O.: "Probleme der physiologischen und pathologischen Chemie," 1913, Leipzig, p. 605.

[5] Ackroyd, H., and Hopkins, F. G.: Biochem. J., 1916, **10,** 551; Geiling, E. M. K.: J. Biol. Chem., 1917, **31,** 173; Stewart, C. P.: Biochem J., 1925, **19,** 1101.

[6] Rose, W. C., and Cox, G. J.: J. Biol. Chem., 1924, **61,** 749; *Ibid.*, 1926, **68,** 781.

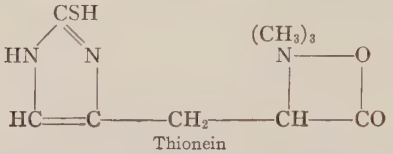
[7] Harrow, B., and Sherwin, C. P.: *Ibid.*, 1926, **70,** 683.

[8] Stewart, C. P.: Biochem. J., 1925, **19,** 266.

is markedly diminished. Addition of arginin to the diet results in no increase in allantoin excretion. This suggests that it is histidin which functions as a precursor of purins.

Cox and Rose[1] have also demonstrated that purins, creatinin and creatin, cannot replace histidin in the diet for purposes of growth. Hence the process histidin → purin is not reversible in the body. Nor is histidin a precursor of creatin in.[2]

S. R. Benedict, Newton, and Behre[3] have recently discovered a new sulphur-containing compound *thionein* (first called thiasin) in hog and human blood and contained wholly in the corpuscles. It was found to be identical with ergothionein, found in ergot, and is the betain of thiolhistidin,[4] a substance with the following formula:



Thionein

A liter of hog's blood contains 145 mg. and a liter of human blood 100 to 250 mg. of thionein.[5] The significance of the substance is as yet unknown.

Prolin, $NH.CH_2.CH_2.CH_2.CH.COOH$.—*Present in most proteins. Three carbon atoms enter into the formation of glucose.*

Dakin[6] gave prolin to a phlorhizinized dog and found extra glucose eliminated to the extent of three of the five carbon atoms contained in prolin. Ringer suggests that the intermediary product may be succinic acid, but lactic acid or glyceric acid are also possible. The metabolism probably follows the same lines as does that of glutamic acid (see p. 243).

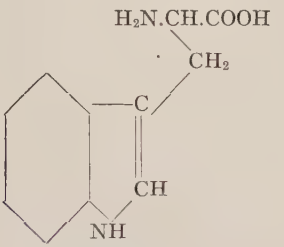
Tryptophan (*Formula below*).—*Present in animal proteins except gelatin. Absent in zein. Produces neither glucose nor β-oxybutyric acid, but is convertible into kynurenic acid.*

Dakin[7] could find no certain increase in sugar or β-oxybutyric acid excretion after giving 14.5 grams of tryptophan to a phlorhizinized dog.

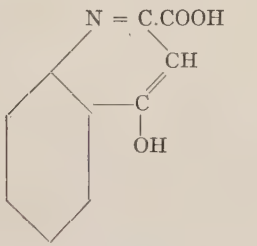
[1] Cox, G. J., and Rose, W. C.: J. Biol. Chem., 1926, **68,** 769.
[2] Steudel, H., and Freise, R.: Z. physiol. Chem., 1922, **120,** 244.
[3] Benedict, S. R., Newton, E. B., and Behre, J. A.: J. Biol. Chem., 1926, **67,** 267.
[4] Newton, E. B., Benedict, S. R., and Dakin, H. D.: Science, 1926, **64,** 602.
[5] Newton, E. B., and Benedict, S. R., and Dakin, H. D.: J. Biol. Chem., 1927, **72,** 367.
[6] Dakin, H. D.: *Ibid.*, 1912–13, **13,** 513.
[7] Dakin, H. D.: *Ibid.*, 1913, **14,** 321.

Ellinger[1] discovered that the production of kynurenic acid, which had long been known as a component of dog's urine, was largely increased after giving tryptophan. Mendel and Jackson[2] found that the kynurenic acid elimination in dogs varied directly with the protein metabolism, but was not derived from gelatin metabolism. Ellinger also gave tryptophan to a rabbit, whose urine normally contains no kynurenic acid, and found kynurenic acid in the urine. Rabbits however, normally oxidize kynurenic acid when ingested in small amounts. He reaches the conclusion that animals in general may produce kynurenic acid, and that this is usually readily oxidized except in the organism of the dog, where it is only partly destroyed, and therefore appears in the urine.

Hopkins and Cole[3] first isolated tryptophan in a state of purity and determined its formula. Miss Homer[4] determined the exact formula of kynurenic acid. Ellinger[5] thus presents the transformation of tryptophan into kynurenic acid:



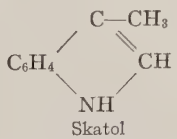
Tryptophan
Indol aminopropionic acid



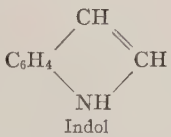
Kynurenic acid
γ-oxy-α-quinolin carboxylic acid

Ellinger and Matsuoka[6] administered indolpyruvic acid to rabbits and, finding kynurenic acid in the urine, concluded that the formation of indolpyruvic acid was the first step in the breakdown of tryptophan. Their formulæ[7] should be consulted for important details.

Intestinal bacteria act upon the propionic acid radicle of tryptophan and convert it into skatol or indol:



Skatol



Indol

[1] Ellinger, A.: Z. physiol. Chem., 1904–05, **43**, 325.
[2] Mendel, L. B., and Jackson, H. C.: Am. J. Physiol., 1898–99, **2**, 1.
[3] Hopkins, F. G., and Cole, S. W.: J. Physiol., 1901–02, **27**, 418.
[4] Homer, A.: J. Biol. Chem., 1914, **17**, 509.
[5] Ellinger, A., and Matsuoka, Z.: Z. physiol. Chem., 1914, **91**, 45.
[6] Ellinger, A., and Matsuoka, Z.: *Ibid.*, 1920, **109**, 259.
[7] Given by Dakin, H. D.: Physiol. Reviews, 1921, **1**, 414.

Indol and skatol, together with phenol, $C_6H_5.OH$, and p-cresol, $CH_3.C_6H_4.OH$, the products of bacterial putrefaction of phenylalanin and tyrosin, are conjugated with sulphuric acid in the liver and are eliminated as ethereal sulphates in the urine (see p. 240).

Summary.—It has been noted that in completely phlorhizinized dogs the actual D:N ratio is 3.65:1. How accurately may one calculate the theoretic origin of glucose from the present amount of information at hand? If the analysis of muscle tissue given by Osborne (see p. 83) be taken, one may estimate how much sugar may arise from the various fragments of the protein molecule.

CALCULATION SHOWING THE ORIGIN OF GLUCOSE FROM PROTEIN

Substance	From 100 Grams of Protein: Amino-acid Grams	Glucose Grams
Glycin	4.0	3.2
Alanin	8.1	8.2
Aspartic acid	10.6	7.2
Glutamic acid	22.3	13.6
Prolin	8.0	6.3
Arginin	11.5	5.9
Cystin*	....	....
Serin*	....	....
	64.5	44.4

* Amount not given.

Since 100 grams of the ox muscle contained 16.18 grams of nitrogen and from this same material 44.4 grams of glucose may be calculated to arise, one may deduce the equation, $D:N = \frac{44.4}{16.18} = 2.75:1$. If the D:N ratio is 3.65, 59 gm. of glucose, or 14.6 gm. more than the quantity above estimated, are eliminated in the urine when 100 gm. of protein are destroyed. These 14.6 gm. represent an additional amount of glucose, whose origin is unexplained and which is equal to 24 per cent. of the total maximal production. Such sources of sugar might be cystin, which, if all the sulphur in protein were in that form, might at most yield 2 grams of glucose, serin whose solubility prevents accuracy of determination, and glycin formed synthetically.

Though the analytic methods are admittedly crude, yet they give some insight into the possibilities of transformation of a heterogeneous medley of amino-acids into a common substance, glucose, the carbohydrate of the organism.[1]

Leucin, tyrosin, and phenylalanin, on the other hand, yield β-oxybutyric acid, or the end-product characteristic of fat metabolism,

[1] Further details, Lusk, G.: Arch. Int. Med., 1915, **15**, 939.

whereas the final products of valin, lysin, histidin, and tryptophan are unknown.

ADDENDUM CONCERNING THE COMPOSITION OF THE URINE

The urine removes the soluble products of metabolism from the organism and the respiration eliminates the gaseous products. The two mechanisms combined maintain the normal reaction of the blood.

In general, the organic constituents of the urine comprise compounds which contain nitrogen. Dakin,[1] however, finds that formic acid, H.COOH, is a constant constituent of urine during fasting, and that the quantity is considerably increased after carbohydrate and after fat ingestion, to a lesser extent also after protein ingestion. He interprets this as signifying that all three food-stuffs yield formic acid as an end-product of their metabolisms. Although the production of formic acid may be considerable, it is so readily oxidizable that it is eliminated in only small amounts in the urine.

The study of creatinin and creatin as excretory products was stimulated by the discovery by Folin of a quick and accurate method of determination.

He gave a diet of milk, cream, and carbohydrate which is free from creatinin and the purin bases, and noted the effect of high and low protein content of the diet on the composition of human urine.

One of Folin's[2] experiments may thus be tabulated, percentages being rendered in black type (see Appendix, p. 764):

INFLUENCE OF HIGH AND LOW PROTEIN DIETS ON THE RELATIVE AMOUNTS OF THE NITROGENOUS CONSTITUENTS OF THE URINE

Food		Composition of the Urine in Grams					
In Grams	In Calories	Total N	Urea N	Ammonia N	Uric Acid N	Creatinin N	Undetermined N
Protein, 118 = 19 N..	2786	16.8	14.70	0.49	0.18	0.58	0.85
Fat, 148.....			**87.5%**	**3.0%**	**1.1%**	**3.6%**	**4.9%**
Carbohydrate, 225....							
Protein, 6 = 1 N.....	2153	3.6	2.20	0.42	0.09	0.60	0.27
Fat, 52.....			**61.7%**	**11.3%**	**2.5%**	**17.2%**	**7.3%**
Carbohydrate, 400....							

A study of this table will reveal the fact that if a man ingest a diet containing a medium amount of protein, and again one that is

[1] Dakin, H. D., Janney, N. W., and Wakeman, A. J.: J. Biol. Chem., 1913, **14**, 341.
[2] Folin, O.: Am. J. Physiol., 1905, **13**, 117.

nearly free from protein, the difference in the character of the urine in the two cases is almost exclusively due to a difference in the output of urea. The quantity of creatinin eliminated remains independent of the quantity of protein metabolized, and the same thing holds true, as a rule, for uric acid (see p. 739). This led Folin to distinguish between an *endogenous* protein metabolism which resulted in the constant and even production of creatinin and was a manifestation of cell metabolism, and an *exogenous* protein metabolism as represented by the urea elimination which is in greater part derived from ingested protein (see p. 739). In reality these correspond quite closely to the "wear and tear" and to the "dynamic" quotas of protein metabolism of Rubner (see p. 360).

Creatinin.—McCollum[1] has observed that pigs may be nourished for long periods of time when fed with a mixture of starch and inorganic salts in sufficient quantity to maintain their weights and energy requirements. After twenty-one to thirty-six days of this diet the relation of creatinin N to total N in the urine was a constant, or 18.5:100. Since the creatinin N has this as an invariable constant (when the diet is free from this constituent), it follows that the true minimal endogenous level of protein metabolism might be calculated at any stage of the experiment by multiplying the quantity of creatinin N by 5.5. Nitrogen in excess of this was supposed to be derived from the destruction of "deposit protein" (see p. 358).

The table just given, which shows Folin's urinary figures for the seventh day of a starch-cream diet in man, shows a relationship of 17.2:100 between creatinin N and total N, thus indicating that the principle may be applicable to man.

However Deuel[2] after taking a protein free and carbohydrate rich diet, under which circumstances he reduced the output of urinary nitrogen to the low level of 1.75 gms. per day, found the ratio to be 33:100. The creatinin output during 54 days of the experiment remained virtually a constant (see p. 360).

The daily elimination of a gram or more of creatinin in the urine is certainly of moment.

Creatinin continues to be eliminated after an Eck fistula (p. 626) has been established in a dog,[3] indicating that the liver cannot be all

[1] McCollum, E. V.: Am. J. Physiol., 1911–12, **29**, 210.
[2] Sandiford, I., Sandiford, K., Deuel, H. J. Jr., and Boothby, W. M.: J. Biol. Chem., 1926, **67**, p. xxv.
[3] London, E. S., and Boljarski, N.: Z. physiol. Chem., 1909, **62**, 465.

important in its production. If creatinin be administered with the food it is almost completely eliminated in the urine.[1] The creatinin elimination is not influenced by muscular work,[2] nor by the increased metabolism of body proteins which follows phosphorus poisoning in fasting dogs.[3]

Schulz[4] states that during the actual period of muscular work the creatinin output in the urine is increased, but not during the day when taken as a whole. He thinks that possibly the muscle parts with some of its creatin during work and this creatin is converted into creatinin.

All of these facts seem to indicate that there is a mechanism in the muscles which is constantly active preparing a definite quantity of creatinin. Whether this comes from arginin or not is unknown (see p. 246).

The ingestion of edestin, which is rich in arginin, does not increase the quantity of creatinin in the urine.[5]

Shaffer[6] has proposed the term *creatinin coefficient* to represent the number of milligrams of creatinin nitrogen eliminated per kilogram of body weight in twenty-four hours. He believes this to be an index of muscular development. In 37 normal men the creatinin coefficient was between 8 and 11. In full accord with this theory Tracy and Clark[7] find the creatinin coefficient of 26 normal women students in a professional school to average 5.8. In two athletic women, with unusual muscular development and control through gymnastic exercise, the creatinin coefficients were 9 and 9.8 or the same as in men. Moreover, McLaughlin and Blunt[8] find the range for the creatinin coefficients of women subjects to be well within that shown by Shaffer for normal men.

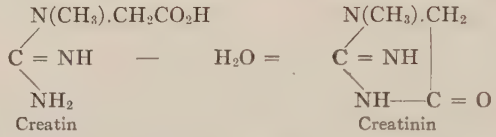
Arguing from the premise that the creatinin metabolism is an index of the quantity of active protoplasm of muscle tissue, Palmer, Means, and Gamble[9] have compared the basal metabolism of 8 men and 9 women in relation to their output of creatinin. The group of men produced 0.98 calories of heat per milligram of excreted creatinin,

[1] Folin, O.: "Hammarsten's Festschrift," Upsala and Wiesbaden, 1906, p. 1.
[2] Van Hoogenhuyze, C. J. C., and Verploegh, H.: Z. physiol. Chem., 1905, **46**, 415.
[3] Lusk, G.: Am. J. Physiol., 1907, **19**, 461.
[4] Schulz, W.: Pflüger's Arch. gesam. Physiol., 1921, **186**, 126.
[5] Gibson, R. B., and Martin, F. T.: J. Biol. Chem., 1921, **49**, 319.
[6] Shaffer, P.: Am. J. Physiol., 1908–09, **23**, 1.
[7] Tracy, M., and Clark, E. E.: J. Biol. Chem., 1914, **19**, 115.
[8] McLaughlin, L., and Blunt, K.: *Ibid.*, 1923–24, **58**, 285.
[9] Palmer, W. W., Means, J. H., and Gamble, J. L.: *Ibid.*, 1914, **19**, 239.

and the group of women 1.26 calories for the same unit. If the premise is correct, then the mass of active protoplasm is not a factor in the measurement of the intensity of the basal metabolism (see p. 133).

Major[1] has administered 0.5 gm. of creatinin in a buffered solution intravenously to man and finds that normally 15 to 80 mg. may be eliminated in the urine of the following 15 minutes. In chronic nephritis no rise took place.

Creatin.—Creatinin is the anhydrid of creatin, a constituent of normal muscle. The adult human being contains about 100 gm. of creatin of which 98 per cent. exists in muscle. Fiske and Subbarow[2] report that it exists in muscle in the form of phospho-creatin, which yields inorganic phosphate when muscle is stimulated. Creatin by treatment with acid is converted into creatinin as follows:



Creatin Creatinin

The close chemical relation between these two substances has led to a search into the problem of their physiologic interrelation.

Myers and Fine[3] report the following creatin content of muscle in various species:

Man	0.39	per cent. creatin.
Dog	0.37	" "
Cat	0.45	" "
Rabbit	0.52	" "

Hunter[4] has collected from the literature details regarding the influence of age on the creatin content of striated muscle as follows:

Rabbit		Man	
Age	Muscle Creatin	Age	Muscle Creatin
	Per Cent.		Per Cent.
Fetal	Trace		
7 days	0.19	At birth	0.19
9 "	0.23	1 yr., 9 mos.	0.33
19 "	0.32	Adult	0.43
39 "	0.39		
Adult	0.43		

[1] Major, R. H.: Arch. Int. Med., 1924, **33**, 89.
[2] Fiske, C. H., and Subbarow, Y.: Science, 1927, **65**, 401.
[3] Myers, V. C., and Fine, M. S.: J. Biol. Chem., 1913, **14**, 9.
[4] Hunter, A.: Physiol. Rev., 1922, **2**, 590.

The quicker and the more efficiently the muscle contracts, the more creatin it possesses. Beker[1] found in the non-pregnant human uterus 0.05 per cent. of creatin, in the uterus at term 0.09 per cent., and in the uterus *postpartum* again 0.05 per cent.

Riesser[2] reports that the quantity of creatin in muscle varies with the quantity of lactacidogen (p. 334) therein, but that rigor mortis or rigor caloris or phosphorus poisoning, all of which reduce the amount of lactacidogen, leaves the quantity of muscle creatin unchanged. Although an accompaniment of muscular efficiency, it is not utilized in the process of muscular contraction.

Muscular fatigue leaves the creatin content of dog's muscle unchanged from the normal.[3]

Folin conceived that creatin and creatinin were biologically independent of each other. The work of S. R. Benedict, however, has presented very conclusive evidence that creatin may pass into creatinin. In the first place Behre and Benedict[4] could find no detectable quantity of creatinin in the blood and they suggested that the creatin found in the blood was essentially a waste product which was quite possibly transformed in the kidney into creatinin and there secreted. Later Benedict and Osterberg[5] found that after the ingestion of creatin about 30 per cent. could be recovered as creatinin in the urine. The process is very slow. Chanutin[6] has confirmed these results and believes that if small quantities of creatin are given they are absorbed by the muscle with subsequent slow elimination in the form of creatinin.

Folin[7] and F. G. Benedict[8] first reported the presence of creatin in the urine of fasting men and offered the hypothesis that it arose from disintegrating muscle tissue. Cathcart[9] independently made the same observation, but witnessed the disappearance of creatin from the urine of the fasting man after giving him carbohydrate, and first suggested that carbohydrate metabolism was associated with creatin oxidation. Mendel and Rose[10] reached the same conclusion.

[1] Beker, J. C.: Z. physiol. Chem., 1913, **87,** 21.
[2] Riesser, O.: *Ibid.*, 1922, **120,** 189.
[3] Mellanby, E.: J. Physiol., 1908, **36,** 447; Scaffidi, V.: Biochem. Z., 1913, **50,** 402.
[4] Behre, J. A., and Benedict, S. R.: J. Biol. Chem., 1922, **52,** 11.
[5] Benedict, S. R., and Osterberg, E.: *Ibid.*, 1923, **56,** 229.
[6] Chanutin, A.: *Ibid.*, 1926, **67,** 29.
[7] Folin, O.: "Hammarsten's Festschrift," Upsala and Wiesbaden, 1906.
[8] Benedict, F. G.: Carnegie Institution of Washington, Pub. 77, 1907, p. 386.
[9] Cathcart, E. P.: J. Physiol., 1906–07, **35,** 500.
[10] Mendel, L. B., and Rose, W. C.: J. Biol. Chem., 1911–12, **10,** 213.

The appearance of creatin in the urine in various other conditions has been attributed to the elimination of creatin liberated through muscle breakdown, but may be partly explained as due to lack of carbohydrate metabolism. Among the conditions reported in which creatin appears in the urine are phosphorus poisoning,[1] carcinoma of the liver,[2] during the period of the involution of the uterus after parturition[3] and also immediately before parturition.[4]

However, Mellanby[5] has shown that caesarean section with removal of the uterus is followed by the same excretion of creatin as after normal parturition. Morse[6] confirms these observations.

That creatin elimination is not an index of cellular destruction was beautifully shown by Stanley Benedict,[7] who maintained a phlorhizinized and fasting dog nearly in nitrogen and weight equilibrium by feeding it with washed meat. The results are given below:

CREATIN EXCRETION IN A PHLORHIZINIZED DOG IN N EQUILIBRIUM

	Weight	N in Food	N in Urine	N Loss from Body	Creatin N	Creatinin N	D: N
	Kg.	Grams	Grams	Grams	Grams	Grams	
Third day fasting.....	7.62	.....	2.74	−2.74	0.075	0.075	
Fourth day fasting: phlorhizin.....	7.58	.....	6.34	−6.34	0.110	0.074	3.9
Second day phlorhizin...	7.44	12.00	11.91	−1.21	0.154	0.071	3.4
Fifth day phlorhizin....	7.08	13.46	12.79	−1.23	0.131	0.070	3.2

On account of the maintenance of the quantity of body protein the creatinin excretion remained constant, but in spite of this maintenance there was a large elimination of creatin. At the completion of the experiments analysis of the muscle-cells showed more rather than less than the normal content of creatin. These are the only experiments which demonstrate an elimination of creatin without a corresponding loss of body tissue or loss of muscle creatin. Stanley Benedict concludes that the creatin elimination is due to complete carbohydrate starvation, that under normal conditions creatin is probably formed in the organism in relatively large amounts, and is

[1] Lefmann, G.: Z. physiol. Chem., 1908, **57**, 476.
[2] Van Hoogenhuyze, C. J. C., and Verploegh, H.: *Ibid.*, 1908, **57**, 161. Also Mellanby, E.: J. Physiol., 1907–08, **36**, 447.
[3] Shaffer, P.: Am. J. Physiol., 1908–09, **23**, 14.
[4] Murlin, J. R.: *Ibid.*, 1909, **23**, p. xxxi.
[5] Mellanby, E.: Proc. Roy. Soc., London, B, 1912, **76**, 88.
[6] Morse, A : J. Am. Med. Assn., 1915, **65**, 1613.
[7] Benedict, S. R., and Osterberg, E.: J. Biol. Chem., 1914, **18**, 195.

for the most part utilized or destroyed when carbohydrate is being oxidized as well.

A long-continued carbohydrate diet which is free from protein reduces the quantity of creatin present in muscle tissue.[1]

A curious phenomenon is the liability of women to creatinuria.[2] M. S. Rose[3] finds that the intermittent creatinuria which occurs in women bears no relation to the sexual cycle. Read[4] reported that the urine of a Chinese eunuch contained much creatin and saw in this the development of the feminine type, but the finding is denied by Shen.[5]

Summarizing the known data, it appears that creatinin is not oxidized in the organism, but if formed is probably completely eliminated in the urine, whereas creatin is continuously produced in quantities above the amount indicated by the creatinin in the urine. In the presence of carbohydrate oxidation this excess of creatin may be destroyed without conversion into creatinin, but in the case of carbohydrate starvation may be eliminated as such in the urine. This opinion has the support of S. R. Benedict.

Uric Acid.—See Chapter on Purin Metabolism.

THE REACTION OF URINE AND BLOOD

Ammonia.—Friedrich von Müller[6] was the first to affirm that the number of grams of ammonia eliminated by an organism during twenty-four hours might be used as an indicator of the intensity of acid formation within the body. Infection of the bladder leading to ammoniacal fermentation has sometimes caused erroneous deductions to be drawn from experimental data. Murlin and Bailey[7] found that the bladder, especially in women, could be irrigated to advantage with a warm saturated solution of boric acid in order to avoid this complication.

To understand the conditions under which ammonia appears in the urine, one must understand the mechanism by which the blood is constantly held at a point the very slightest degree on the alkaline side of neutrality.

[1] Myers, V. C., and Fine, M. S.: J. Biol. Chem., 1913, **15**, 305.
[2] Krause, R. A.: Quart. J. Exper. Physiol., 1911, **4**, 293; Denis, W., and Minot, A. S.: J. Biol. Chem., 1917, **31**, 561.
[3] Rose, M. S.: J. Biol. Chem., 1917, **32**, 1.
[4] Read, B. E.: *Ibid.*, 1921, **46**, 281.
[5] Shen, T. C.: Proc. Soc. Exper. Biol. and Med., 1925, **22**, 408.
[6] von Müller, F.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, 261.
[7] Murlin, J. R., and Bailey, H. C.: Arch. Int. Med., 1913, **12**, 288.

Distilled water is absolutely neutral in reaction, that is to say, the number of free H^+ ions is equal to the number of free hydroxyl (OH) ions.[1] A normal solution of hydrochloric acid contains 1 gram of hydrogen in a liter of water at which concentration it is not wholly ionized, whereas in pure distilled water only one-ten-millionth of a gram of free hydrogen ions is present. Solutions are acid which have more than one-ten-millionth of a gram of hydrogen ions in a liter. They become alkaline when the hydrogen ion concentration falls below this point, which for convenience may be written 10^{-7}. Thus, when the hydrogen ion concentration is one part in one hundred million or 10^{-8} the hydroxyl concentration represents one-millionth normal alkaline solution. The hydrogen ion concentration of the blood varies between 10^{-7} (which it reaches only in severe acidosis) and 10^{-8}, which is attained only after the administration of alkalies.

The addition of one-millionth of a gram of hydrogen ions (which would be contained in 36.5-millionths of a gram of hydrochloric acid) to a liter of water would change its hydrogen ion concentration of 10^{-7} to one of less than 10^{-6}. Some cells cannot live in this concentration of acid.

In order to abolish cumbersome numbers, such as 0.35×10^{-7}, Sörensen suggested that the negative exponent be used as a whole number. This is called the hydrogen ion exponent or pH.

$N/10$ acid $= 10^{-1}$	pH = 1
$N/1{,}000{,}000 = 10^{-6}$	pH = 6
$N/500{,}000 = 2 \times 10^{-}$	pH = 5.70
(log. 2 = 0.3;	$-6 + 0.3 = -5.70$)
$N/28{,}580{,}000 = 0.35 \times 10^{-7}$	pH = 7.45

The last figure given above represents an acid solution of three ten-millionths normal, or the equivalent of 0.000012 gram of NaOH dissolved in a liter of water. This is the usual alkalinity of the blood, and, though so slight that it may almost be called neutrality, is yet of definite importance.

McClendon,[2] after careful experimentation, concludes that the normal pH of venous blood is 7.5, with a range between 7.45 and 7.55. The extreme difficulty of the technic renders the reports of many experimenters only relatively accurate.

[1] Consult Michaelis, L.: "Die Wasserstoffionenkonzentration," Berlin, 1914.
[2] McClendon, J. F., and Magoon, C. A.: J. Biol. Chem., 1916, **25**, 669.

The use of logarithms as expressive of acidity requires a little practice to accustom oneself to think, for example, that pH = 5.70 represents a solution whose acidity is twice that represented by pH = 6. Also, it must be remembered that the smaller the figure, the higher the concentration of hydrogen ions.

To Lawrence J. Henderson[1] belongs the credit of the following analysis: The proper action of physiologic processes depends on the accurate adjustment and preservation of temperature, molecular concentration, and neutrality. Within the organism there is a constant formation of acid substances, principally carbonic, sulphuric, and phosphoric acids, which immediately combine either wholly or in part, according to their several avidities, with the basic constituents of the protoplasm and blood. In pathologic conditions β-oxybutyric acid and aceto-acetic acid claim their share of base. Metabolism, therefore, operates to lower the unvarying alkaline reaction of the blood. This reaction, according to Henderson, is maintained under conditions in which 89 per cent. of the phosphates of the blood are dibasic, as in Na_2HPO_4, and 11 per cent. monobasic, as in NaH_2PO_4, and in which 93 per cent. of the carbon dioxid is present in $NaHCO_3$, and 7 per cent. free as free CO_2. Henderson states that the arrangement of these four substances in the blood is such that the whole system surpasses in efficiency any possible closed aqueous solution of like concentration for preserving the hydrogen ion concentration of the blood at the normal of 0.3×10^{-7}.

If an acid be introduced into this system, not only may monosodic phosphate be formed from disodic phosphate or additional amounts of CO_2 dissociated from sodic bicarbonate, but both these acid substances may be eliminated by the kidney and lungs respectively, thereby maintaining the reaction at a normal level. The high diffusibility of these acid products assists in this regulation.

If alkali increases in the system, this though converted into bicarbonate must necessarily be accompanied by a large increase in osmotic pressure. The elimination of an alkaline urine corrects this.

Carbonic acid is lost through the lungs without loss of alkali to the body.

Phosphoric and sulphuric acids are removed from the blood by the kidney in the forms of NaH_2PO_4 and Na_2SO_4. If they were

[1] Henderson, L. J.: Ergeb. d. Physiol., 1909, **8**, 254; J. Biol. Chem., 1911, **9**, 403.

removed in other forms the urine would be intensely acid. The ordinary acid formation in the human organism corresponds to between 600 and 700 c.c. of N/10 acid solution daily.[1] On account of the bases in combination the actual pH in 222 specimens of urine for twenty-four hours from 16 individuals showed an average value of 5.98, the range being between 5.1 to 7.[2] For a short period the urine may be as alkaline as 7.4. Blatherwick[3] finds the average pH of 30 urines of vegetarians to be 6.63. The *titratible acidity* appears to be a function of the ionized hydrogen present, and is almost wholly due to the excess of primary phosphate over secondary phosphate.

The quantity of ammonia, though it presents a clear gain of so much alkali for the body, does not appear to vary for purposes of regulating the reaction of the blood. The main regulation is accomplished by the elimination of acid phosphate and carbon dioxid. Only in pathologic conditions with acid formation is ammonia drawn upon for purposes of regulation.

The body's reserves of alkali are considerable, and replenishment is usually accomplished through alkalis contained in the food (see p. 484).

According to Michaelis,[4] the reaction of the fluid which may be expressed from fresh tissues and thrown in boiling water to prevent postmortal acid formation is not alkaline like blood, but is almost exactly neutral.

Bearing in mind the fundamental factors presented above, one may now consider the actual results of administering acids or alkalies upon the composition of the urine and blood.

In the first place, it was shown by Haldane and Priestley[5] that a very small increase in the tension of carbon dioxid in the alveolar air was accompanied by a stimulation of the respiratory center. Krogh and Krogh[6] proved that the tension of carbon dioxid in the alveoli closely follows that of arterial blood. Finally, Hasselbalch[7] showed that in reality an increase in the hydrogen ion concentration of the blood was the real stimulus to respiration, and thus caused the blood to be automatically relieved of excess of acid ions existing in the form

[1] Henderson, L. J., and Palmer, W. W.: J. Biol. Chem., 1913, **14**, 81.
[2] Henderson, L. J., and Palmer, W. W.: *Ibid.*, 1914, **17**, 305.
[3] Blatherwick, N. R.: *Ibid.*, 1914, **17**, p. xl.
[4] Michaelis, L., and Kramsztyk, A.: Biochem. Z., 1914, **62**, 180.
[5] Haldane, J. S., and Priestley, J. G.: J. Physiol., 1905, **32**, 225.
[6] Krogh, A., and Krogh, M.: Skan. Arch. Physiol., 1910, **23**, 179.
[7] Hasselbalch, K. A.: Biochem. Z., 1912, **46**, 403.

of $\overline{HCO_3}$. In experiments he showed that when an acid urine was being secreted the CO_2 tension of the alveolar air was lowered, indicating increased acid in the blood. A diet which produced a less acid or an alkaline urine increased the CO_2 tension of the alveolar air, indicating a larger content of alkali in the blood.

The figures for one experiment may be here reproduced:

	Alveolar CO_2 Tension in Mm. Hg	pH of Blood	
		At 40 Mm. CO_2 Tension	At Alveolar CO_2 Tension
Meat diet	38.9	7.33	7.34
Vegetarian diet	43.3	7.42	7.36

In another experiment a larger volume of respiration was found to accompany the lower alveolar CO_2 tension, as follows:

	Alveolar CO_2 Tension in Mm. Hg	Alveolar Ventilation. Liters per Minute at 37 Degrees
Meat diet	38.5	4.40
Vegetarian diet	43.1	4.08

These results demonstrate that CO_2 acts only indirectly upon the respiratory center. For the maintenance of a constant reaction of the blood, more CO_2 is required in the presence of alkali than in the presence of acid. The variation in the ventilation of the lungs, brought about by the sensitiveness of the respiratory center to H ions controls the CO_2 tension in the alveoli, so that the reaction of the blood remains practically unchanged under the two given different dietary conditions.

The matter of the changing sensitiveness of the respiratory center itself has been ably discussed by Gesell.[1]

It is only in exceptional cases that in the normal life of a man at rest the diurnal variation in the carbon dioxid tension of the alveoli exceeds the equivalent of 2 mm. of mercury.[2]

Fleisch[3] has given slow intravenous injections of acid sodium phosphate to rabbits under urethan. The CO_2 tension in the arterial

[1] Gesell, R.: "Chemical Regulation of Respiration." Physiol. Rev., 1925, **5**, 551.
[2] Erdt, H.: Deut. Arch. klin. Med., 1915, **117**, 497; Higgins, H. L.: Am. J. Physiol., 1914, **34**, 114.
[3] Fleisch, A.: Pflüger's Arch. gesam. Physiol., 1921, **190**, 270.

blood fell, as did also the pH and the rate of respiration. Some of his experiments follow:

Exp. No.	Ventilation in 15 Sec.	Arterial Blood	
		CO_2 Tension	pH
	C.C.	Mg. Hg	
I. Preliminary	155	30.4	7.3
After NaH_2PO_4	208	25.1	7.16
II. Preliminary	115	27.3	7.42
After NaH_2PO_4	154	25.1	7.32
III. Preliminary	81	27.7	7.42
After NaH_2PO_4	120	23.1	7.35

The conclusion is drawn that the increase in acidity is the cause of the increase in respiration.

The administration of acid to such an extent that the reaction of the blood becomes acid produces death. Such blood cannot combine with carbon dioxid. Thus, after giving 90 c.c. of half-normal hydrochloric acid intravenously to a dog, death resulted in virtue of the production of an experimental acidosis, the pH equalling 6.9 in the blood.[1] The reduction of carbonic acid in the blood of a rabbit from 45 volumes per cent. to 10.1 per cent., with accompanying dyspnea, was observed by Loewy and Münzer[2] after the administration of 0.72 gram of hydrochloric acid per kilogram of body weight, and Porges[3] has noted that intravenous injection of monosodic phosphate into a narcotized rabbit raises the respiratory quotient from 0.68 to 0.79, indicating the elimination of carbon dioxid from the plasma.

If, however, acid in moderate quantity is given with food, increased ammonia production may neutralize the acid given.

This has been beautifully shown with calves,[4] as appears in the following experiment:

CALF: WEIGHT, 100 KG.; FOOD, 9.1 KG. OF MILK DAILY

Period	No. of Days	N in Food	N in Urine	NH_3—N	Urea N
		Grams	Grams	Per Cent.	Per Cent.
No acid given	9	30.00	12.4	12.8	76.0
220 c.c. normal HCl	6	30.00	12.4	19.4	74.1
330 c.c. normal HCl	7	30.00	11.5	31.7	55.8
500 c.c. normal HCl	3	30.00	12.9	37.0	43.1

[1] Levy, R. L., Rowntree, L. G., and Marriott, W. McK.: Arch. Int. Med., 1915, **61**, 389.
[2] Loewy, A., and Münzer, E.: Arch. f. Physiol., 1901, p. 81.
[3] Porges, O.: Biochem. Z., 1912, **46**, 1.
[4] Steenbock, H., Nelson, V. E., and Hart, E. B.: J. Biol. Chem., 1914, **19**, 399.

Only when the larger quantities of acid were administered did it appear that the bones were attacked, and this was at the expense of their calcium carbonate content. The administration of acid did not prevent the growth and development of the calf.

In man hydrochloric acid may be given with a similar protective rise of ammonia, as appears below:[1]

CONSEQUENCE OF ADDING HYDROCHLORIC ACID TO THE DIET OF MAN. DAILY AVERAGES

	No. of Days	Alveolar Tension		Urine			
		CO_2	O_2	N	NH_3	P_2O_5	Cl
		Per Cent.	Per Cent.	Grams	Grams	Grams	Grams
Normal diet	3	6.00	5.10	13.50	0.92	1.92	4.28
Same + HCl	3	5.98	5.36	13.65	1.59	2.15	7.92

In the above experiment 85 c.c. of a solution containing 12 per cent. or 10.2 grams of chlorin was added to the food during three days, being an average of 3.4 grams of chlorin per day. This would require 1.6 grams of ammonia to effect its neutralization. On the third day of acid administration the ammonia rose to an output of 2.03 grams. The phosphates increased 12 per cent. and there was a rise in the acidity of the urine. As the result of these protective agencies the carbon dioxid tension in the blood remained unchanged after the administration of hydrochloric acid.

The work of Nash and Benedict[2] has revolutionized the ideas regarding the seat of the formation of ammonia in the body. They found that the ammonia content of the renal vein was double that of arterial blood and they designated the kidney as the seat of ammonia production and urea its source in the animal body. The work has been confirmed by others.[3] Benedict and Nash[4] in a later paper find that there is less ammonia in the body than in most c. p. chemicals. It is made in the kidney for purposes of neutralization. They find that, in spite of high acidosis in the blood and high ammonia excretion in the urine, as occurs in acute diabetes, there is no increase over the normal value of 0.1 mg. of ammonia in 100 cc. of blood. In a phlorhizinized dog the urinary ammonia rises six to eightfold, but the

[1] Begun, A., Herrmann, R., and Münzer, E.: Biochem. Z., 1915, **71**, 255.
[2] Nash, T. P., Jr., and Benedict, S. R.: J. Biol. Chem., 1921, **48**, 463.
[3] Loeb, R. F., Atchley, D. W., and Benedict, E. M.: *Ibid.*, 1924, **60**, 491.
[4] Benedict, S. R., and Nash, T. P., Jr.: *Ibid.*, 1926, **69**, 381.

ammonia content of arterial blood remains unchanged. Russell[1] found a normal content of ammonia in the blood of nephritic patients. Bliss[2] found no increase in the ammonia content of blood which has passed through the liver or the muscles. The neutralization of acids by ammonia, therefore, is not a generalized tissue phenomenon but is a function of the kidney alone. Benedict and Nash believe that the chief objection to this idea is due to its novelty.

Rabinowitch[3] gives the following table showing the average elimination of ammonia per liter of human urine:

	Ammonia per L. Urine
Normal, 16 cases	av. 0.98 gm.
Nephritic, 22 cases	" 0.78 "
Diabetes, no ketosis, no albuminuria, 17 cases	" 0.96 "
Diabetes, ketosis, no albuminuria, 16 cases	" 1.09 "
Diabetes, albuminuria, no ketosis, 22 cases	" 0.75 "
Diabetes, albuminuria and ketosis, 19 cases	" 0.84 "

Rabinowitch concludes that the ammonia content of the urine of nephritic persons is less than that of the urine of normal people. He states that general clinical experience teaches that diabetic persons with nephritis are more susceptible to an acidosis than those with no nephritis and attributes this to the vulnerability of the kidney. This strengthens Benedict's view that the kidneys are the site of ammonia formation.

In certain pathologic states, such as diabetes, phosphorus poisoning, the so-called food intoxication of infants,[4] and other conditions, there is an increased production of ammonia in the kidney for the neutralization of acids of endogenous origin. This may be accompanied by a withdrawal of body alkali, so that the power to combine with carbon dioxid is greatly reduced and the alveolar tension of CO_2 falls in consequence. However, even under these conditions the reaction of the blood may remain unaffected. This is strikingly illustrated in the experiments of Poulton[5] on cases suffering from severe diabetes, in which condition β-oxybutyric acid is largely formed. (See table, p. 661.)

The blood of the first six patients showed a normal pH. Only in the depth of coma a few hours before death is there

[1] Russell, D. S.: Biochem. J., 1923, **17**, 72.
[2] Bliss, S.: J. Biol. Chem., 1926, **67**, 109.
[3] Rabinowitch, I. M.: Arch. Int. Med., 1924, **33**, 394.
[4] Howland, J., and Marriott, W. McK.: Am. J. Dis., Child., 1916, **11**, 309.
[5] Poulton, E. P.: Proc. Physiol. Soc., J. Physiol., 1915–16, **50**, p. 1.

a distinct fall in alkalinity, and, indeed, this fall may not be as great as in a normal person after climbing a thousand feet in twenty-five minutes, under which circumstances the pH may be 7.09 (see p. 422).

It is evident that the reaction of the blood in severe diabetes is maintained at the normal through the reduction of its carbon dioxid content. Such a reduction in carbon dioxid combining power indicates a reduction in the alkali reserve of the blood, and forms the basis of the important method of Van Slyke for investigating the intensity of acidosis.

That ammonia in the urine is an indicator of acid formation and not due to a pathologic disturbance of urea formation was shown by Muenzer,[1] who gave alkali in cirrhosis of the liver and reduced the quantity of ammonia elimination to normal. Fiske and Karsner[2] find that livers which have been severely damaged in the living animal by administration of chloroform, phosphorus, hemolytic immune sera, hydrazin sulphate, or phlorhizin still preserve the power of transforming perfused ammonium carbonate into urea. Janney,[3] in von Müller's laboratory, gave bicarbonate of sodium to men and found that the quantity of ammonia in the urine was reduced to almost undeterminable traces; hence the ammonia in the urine has as its sole function the neutralization of acid bodies and ceases to be formed in the presence of an excess of fixed alkali.

Marriott and Howland[4] demonstrated that in *nephritis* inorganic phosphates accumulated in the blood coincident with the development of acidosis. In the acidosis characteristic of nephritis there is no increase in the ammonia content of the urine. Although the administration of 500 cc. of decinormal hydrochloric acid to a man results in a great increase of ammonia in the urine, even 1500 cc. decinormal monosodic phosphate leads to absolutely no increase in the urinary ammonia, although there is a great increase in the titratable acid in the urine. Such conditions are like those reported as being characteristic of nephritic urine.

Klein and Moritz[5] found that on the day following a diet which was rich in fat there was an increase in the quantity of fixed alkali in

[1] Muenzer, E.: Deut. Arch. klin. Med., 1894, **52,** 199 and 417.
[2] Fiske, C. H., and Karsner, H. T.: J. Biol. Chem., 1914, **18,** 381.
[3] Janney, N.: Z. physiol. Chem., 1911–12, **76,** 99.
[4] Marriott, W. McK., and Howland, J.: Arch. Int. Med., 1918, **22,** 477.
[5] Klein, W., and Moritz, F.: Deut. Arch. klin. Med., 1910, **99,** 162.

the urine and a corresponding fall in the quantity of ammonia. They interpret the results as signifying that the alkali was temporarily involved in fat metabolism (formation of soaps) and was eliminated when this need was no longer present.

The consideration of the ingestion of alkalies and bases in the food will be discussed in the chapter on A Normal Diet.

CHAPTER XI

THE INFLUENCE OF PROTEIN FOOD (Continued)

PART III—THE RESPIRATORY METABOLISM

Set me fine Spanish tables in the hall
See they be fitted all;
Let there be room to eat
And order taken that there want no meat.

English Verse of about 1600.

The discussion of the more important details of the breakdown of amino-acids in the organism reveals the beginning of modern mental penetration into the biochemical reactions in the organism. However, the gross results of protein ingestion are to be ascertained by other means, by a study of the respiratory metabolism and by calorimetric observations.

Bidder and Schmidt[1] gave meat to the full extent of its appetite to a cat which had previously been starved and reported the following figures for the respiratory exchange:

	CO_2 Grams	O_2 Grams	R. Q.
Fasting	53.52	50.18	0.77
Excessive meat ingestion	113.52	103.84	0.80

Many subsequent experiments have brought to light this characteristic increase in metabolism after the ingestion of protein in excess.

As carnivorous animals will take meat in large amounts, its influence is best studied in experiments upon them.

THE PRODUCTION OF SUGAR FROM PROTEIN

In 1862 Pettenkofer and Voit (see p. 189) noted that after giving meat in large quantity a portion of the carbon of the protein metabolized was retained in the body, which they interpreted as indicating a production of fat from protein. Frank and Trommsdorff[2] and also Rubner[3] gave meat in large amount to dogs, and determined the

[1] Bidder, F., and Schmidt, C.: "Verdauungssäfte und Stoffwechsel," Mitau and Leipzig, 1852, p. 356.
[2] Frank, O., and Trommsdorff, R.: Z. f. Biol., 1902, **43**, 266.
[3] Rubner, M.: "Energiegesetze," 1902, p. 365.

carbonic acid output of the animals during invervals lasting between three and six hours. The first named authors noted that although the urinary nitrogen elimination showed a maximum rise of nearly eight times that of fasting and varied greatly, the carbonic acid elimination was not so largely increased and was much more even.

The details of the results following the ingestion of large quantities of meat by a dog are to be found in the calorimetric observations of Williams, Riche, and Lusk.[1] These authors made observations in hourly periods upon the nitrogen in the urine, the carbonic acid elimination and oxygen absorption, and the heat production of a dog following the ingestion of 1200 grams of meat. The results are in part presented in the accompanying curve:

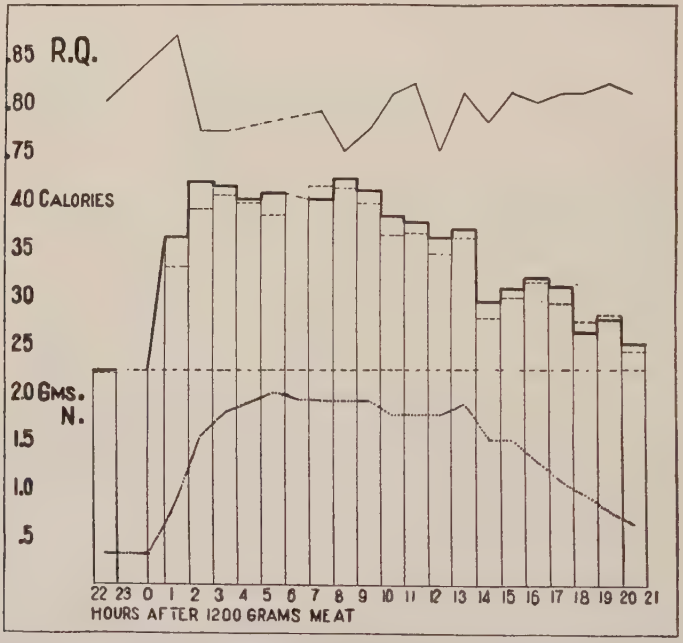


Fig. 16.—Showing the R. Q., the total metabolism determined by indirect (heavy black line) and direct (broken line) calorimetry, as well as the nitrogen elimination (dotted line), during hourly periods after the ingestion of 1200 grams of meat.

During the fourth hour the nitrogen in the urine reached a level of 1.80 grams and remained between 1.76 and 2 grams per hour during a period of eleven hours. During this period the heat production was nearly twice the normal basal metabolism, and the

[1] Williams, H. B., Riche, J. A., and Lusk, G.: J. Biol. Chem., 1912, **12**, 349.

increase was proportional to the increase in protein metabolized as calculated from the increased nitrogen elimination above that of the basal metabolism. However, during the second and third hours, in which the increase in heat production almost reached its maximum, the urinary nitrogen was only 0.89 and 1.55 grams respectively. This is due to the fact that urea was accumulating in the blood and the quantity of its elimination in the urine did not at first truly represent the intensity of the metabolism of protein (see p. 208). This fact is made certain by the curve of glucose and nitrogen elimination obtained by Janney[1] after giving serum albumin to a phlorhizinized dog (see p. 294). In this curve the glucose elimination reached its maximum during the first hour, the nitrogen elimination during the fifth. It seems also probable that after giving 1200 grams of meat to the normal dog the establishment of a plateau of even nitrogen elimination indicates that during this period the influx of protein nitrogen from the intestine equalled its destruction within the cells and its outgo through the urine. When a fall in the nitrogen output set in, the metabolism also fell as the result of the decrease in protein metabolism.

During an experimental period of twenty-two hours the heat production calculated from the excreta was 738.5 calories, and directly measured by the calorimeter was 718.5 calories, a difference of 20 calories, or 2.7 per cent. During the first two experimental hours there was always a considerable discrepancy between indirect and direct calorimetry. It is now certain that this was due to the fact that the meat was given when cold (see p. 158). Allowing for this error, the indirect and direct methods agree within less than 2 per cent.

An interesting fact revealed in the analysis of the respiratory exchange is that, beginning with the second hour and continuing for fourteen hours after the ingestion of protein, the respiratory carbon dioxid is less than that which one would expect if all parts of the protein complex were oxidized. There is, therefore, *carbon retention* during this period. Such carbon might have been retained in the form of carbohydrate or of fat. Schreuer[2] gave 900 and 1500 grams of meat to a dog and determined the metabolism by the Zuntz method from three to four hours after meat ingestion. He concluded from

[1] Janney, N. W.: J. Biol. Chem., 1915, **20**, 329.
[2] Schreuer, M.: Pflüger's Arch. gesam. Physiol., 1905, **110**, 227.

the respiratory quotient that carbon derived from protein was retained in the form of carbohydrate. New confirmation of the conversion of part of the protein molecule into glucose was afforded by the oxygen absorption of the dog of Williams, Riche, and Lusk during various periods following the ingestion of 1200 grams of meat. These facts are here set forth:

TABLE CONTRASTING THE ACTUAL OXYGEN INTAKE WITH THAT REQUIRED BY THEORY IF THE CARBON RETENTION HAD BEEN IN THE FORM OF GLYCOGEN OR OF FAT. 1200 GRAMS MEAT INGESTED AT NOON

Time	Calories		C Retained (Calc. as Glucose)	O_2 Actual	O_2 (C Retained as Glucose)	O_2 (C Retained as Fat)
	Found	Calculated				
P. M.			Gm.	Gm.	Gm.	Gm.
1.45– 2.45	38.92	41.70	0.10	13.63	12.99	12.95
2.45– 3.45	40.40	41.29	1.93	13.29	12.56	11.73
3.45– 6.45	121.91	124.82	7.86	43.25*	40.61	37.23
6.45– 9.45	122.11	122.86	7.86	40.35	40.01	36.63
9.45–12.45	106.70	111.67	7.50	35.47	36.41	33.19
12.45– 1.45	35.86	36.82	3.42	11.34	12.13	10.66
1.45– 2.45	27.71	29.32	2.75	9.31	9.65	8.47
2.45– 4.45	61.24	62.36	3.08	19.56	20.19	18.87
	554.85	570.84	34.50	186.20	184.55	169.73
	Dif. = 2.8%			Dif. = 0.9%		Dif. = 10%

34.5 grams glucose: 28.3 grams N:: 1.2: 1

* Small leak in the apparatus during this period determined the day following to amount to about 1 gram O_2 per hour.

The respiratory quotients (see Fig. 16) fall during the hours of carbon retention to below that of protein itself (which is 0.80), because the unoxidized carbohydrate is retained in the organism as glycogen. If the carbon were retained in the organism as fat, the respiratory quotient would rise. If one considers the period between the hours of 6.45 and 9.45 P. M., one obtains the following picture of what occurs:

METABOLISM OF A DOG DURING A THREE-HOUR PERIOD OF MAXIMAL PROTEIN CARBON RETENTION AFTER 1200 GRAMS MEAT

	Direct	Indirect (C Retained = 3.14 Grams)	
		If Retained as Glucose	If Retained as Fat
Calories	122.11	122.86	113.32
Oxygen, grams	40.35	40.01	36.63
Respiratory quotient	0.77	0.77	0.85

It is obvious from these figures that *the oxygen absorption and the heat production prove the retention of carbon either in the form of glucose or glycogen in the organism.* During the fourteen hours of carbon retention following the ingestion of 1200 grams of meat, the actual oxygen absorption was 186.2 grams against a value of 184.5, calculated on the assumption that carbon was stored as glycogen or a difference of 0.9 per cent. If the carbon had been retained as fat, 169.7 grams of oxygen would have been required, or 10 per cent. less.

During these fourteen hours 34.5 grams of glucose were stored as glycogen in the organism and 28.3 grams of N were eliminated in the urine. This yields a D:N ratio of 1.2:1. Since 3.6 is the maximum yield of glucose per gram of N in diabetic urine, it is evident that one-third of the glucose derivable from protein in metabolism was retained in the organism and deposited in the liver and other glycogen reservoirs. This represents 20 per cent. of the total energy contained in the protein metabolized.

Another illustration of this phenomenon was discovered by McCann,[1] who showed that the administration of the protein of meat to a normal man on the 11th day of starvation resulted in the initial establishment of respiratory quotients of 0.68 in two successive hourly periods. These quotients are obtainable only in severe diabetes when glucose derived from protein cannot be oxidized. It may be possible that the fasting man with a depleted glycogen store, receiving protein, retained as glycogen that part of protein which is convertible into glucose and did not at first oxidize it.

The production of glucose from protein is not an emergency process as some writers maintain; it is a normal function.

THE PRODUCTION OF FAT FROM PROTEIN

A question which has aroused great interest is that concerning the production of fat from protein. Pettenkofer and Voit[2] found that after ingesting considerable quantities of protein, although the nitrogen of the protein was eliminated in the urine, a part of the carbon was retained in the body and not excreted by the usual channels. They estimated that meat protein contained 3.68 grams of carbon to each gram of nitrogen. If less than 3.68 grams of carbon appeared in the total excreta when 1 gram of nitrogen was eliminated, then

[1] McCann, W. S.: Proc. Soc. Exper. Biol. and Med., 1919–20, **17**, 173.

[2] Pettenkofer, M., and Voit, C.: Ann. Chem. u Pharm., 1862, **2**, Suppl., pp. 52 and 361; Z. f. Biol., 1871, **7**, 433.

some protein carbon must have been stored in the body. This carbon might have been retained in two forms—as glycogen or as fat. Claude Bernard had shown that glycogen increases in the liver after the ingestion of protein. The retained carbon as observed by Pettenkofer and Voit was in such large quantity as to preclude the possibility of its retention entirely as glycogen, and therefore they concluded that fat must have been prepared from protein and stored up in the body. This afforded an experimental basis for the theory of a production of fat from protein in fatty degeneration.

Later Rubner,[1] in Voit's laboratory, showed that the relation 3.68 C : 1 N in protein, as used by Pettenkofer and Voit, was inaccurate, and that meat fully extracted with ether contains only 3.28 of carbon to one of nitrogen (see p. 84). The polemical arraignment by Pflüger[2] of Voit's older work was based upon these results of Rubner. Instead of there being a great retention of protein carbon, there was none in some experiments and very little in others. The formation of fat from protein was evidently less easy of demonstration than it had seemed.

The subject was investigated anew by Cremer,[3] who starved a cat for many days, and then gave the animal all the lean meat it would eat, or about 450 grams a day. The cat was kept in a respiration apparatus and the total excreta were collected. The carbon belonging to the meat ingested was calculated at the low ratio of 3.2 to 1 of nitrogen. The average daily metabolism during the eight days of meat ingestion is indicated in the following table:

	WEIGHTS IN GRAMS				
N in Urine and Feces	Urine	C in Feces	Respiration	Meat C Calculated from N Excreted	C from Meat Added to the Body
13.0	7.5	1.4	25.4	41.6	7.3
		34.3			

There was a daily excretion of 13 grams of nitrogen corresponding to the liberation of 41.6 grams (13 × 3.2) of protein carbon. But only 34.3 grams of carbon were actually eliminated from the body, and a difference of 7.3 grams was retained in the body; 17.5 per cent. of the protein carbon therefore was not eliminated. For eight days the whole carbon retention was 58 grams, which corresponds to a glycogen production of 130 grams. The cat, however, contained only

[1] Rubner, M.: Z. f. Biol., 1885, **21**, 324.
[2] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1892, **52**, 239.
[3] Cremer, M.: Münchener med. Wochenschr, 1897, **44**, 811; Z. f. Biol., 1899, **38**, 309.

35 grams of glycogen, determined after killing it at the end of the experiment. The balance of the carbon must have been stored as fat.

Cremer[1] notes that a cat fed as above contains 1.47 per cent. of muscle glycogen, which is as much as the maximum (1.37 per cent.) found by E. Voit in geese after the ingestion of starch. One should here recall that Pflüger (see p. 209) found as much as 10 per cent. of glycogen in the liver of a previously fasting dog after it had been fed with codfish. This is as much glycogen as would have been deposited after carbohydrate ingestion.

Since it is known that sugar in excess may be converted into body fat and that meat may yield 58 per cent. of sugar in metabolism, there is every reason to believe that if protein be ingested in excess the deaminized residues of many of the amino-acids may be converted into glycogen, and then, if this pathway be closed through saturation of the body-cells with glycogen, fat is formed instead (see p. 271).

This hypothesis was tested in respiration experiments upon dogs, performed by Atkinson, Rapport, and Lusk.[2] They determined whether measurements of the respiratory quotients and the heat production would indicate a deposition of fat from protein metabolism after excessive meat ingestion. A respiratory quotient of over 0.802 (that of meat) would mean the retention of fat; one below 0.802 a retention of carbohydrate. It is difficult to induce a dog of 10 kg. to take daily a diet of 1100 to 1300 gm. of meat, and only with these quantities is there strong evidence of the conversion of protein into fat as a dominant feature. The dog apparently does not desire meat in such quantity as to enable the production of fat from it. The procedure finally adopted was to give to the animal the "standard maintenance diet," containing 70 gm. of starch, every evening at 5 o'clock in order to charge the glycogen repositories. Then at 9 o'clock the next morning 1000 gm. of meat were given and the metabolism determined during the 5th to the 8th hours thereafter which include the hours of the highest protein metabolism. An alcohol check of the respiration apparatus before the experiment showed a respiratory quotient of 0.667 and two days after the experiment one of 0.670 (theory, 0.667). The heat of the burning alcohol as measured (direct) agreed with the heat calculated (indirect) within 1 per cent. The story of the calculation of the fifth hour after

[1] Cremer, M.: Z. f. Biol., 1899, **38**, 313.
[2] Atkinson, H. V., Rapport, D., and Lusk, G.: J. Biol. Chem., 1922, **53**, 155.

giving 1000 gm. of meat to Dog XVIII will suffice as a guide to the method.

URINARY N = 1.44 GM.

	CO_2	O_2	R. Q.	Calories
	Gm.	Gm.		
Equivalent of 1.44 gm. N	13.46	12.23	0.802	38.17
Found in respiration	10.10	8.72	0.842	
Equivalents of the pabulum retained	3.36	3.51	0.700	11.32
Calories (indirect)	.....	.....	.....	26.85
Calories (direct)	.....	.....	.....	27.52

The 3.36 gm. CO_2 computed to belong to the protein metabolism of the time but not eliminated in the respiration was the equivalent of 0.92 gm. C, which corresponds to 1.2 gm. of fat; 0.92 gm. fat C $\times$ 12.31 = 11.32 calories retained as fat. This, deducted from the calories of protein calculated from the urinary nitrogen, gives the total calories calculated. The respiratory quotient of that part of the unoxidized moiety of the protein retained was 0.7, which indicates the retention of fat. If the retained C had been in the form of glucose, 2.3 gm. glucose would have been laid down as glycogen in the body; and glucose, 2.3 gm., = 8.63 calories. If the calories had been retained as glycogen, the calculated heat would have been 38.17 − 8.63 = 29.54.

		Difference
Calories (direct)	27.52	
Calories (indirect) C retained as fat	26.85	−0.77
" " C retained as carbohydrate	29.54	+2.02

The destruction of protein which corresponds to the appearance of 1.44 gm. of nitrogen in the urine involves the possible production of 5.26 gm. of glucose. Of this 44 per cent. was not oxidized but was converted into fat. In another experiment the fat retained amounted to the equivalent of a conversion into fat of 53 per cent. of the potential glucose formation.

When the glycogen reservoirs of a dog are charged by giving a carbohydrate-containing meal in the evening and 1000 gm. of meat in the morning, then during the height of protein digestion both the respiratory quotients and the calorimeter measurements indicate the deposit of a material consisting of fat. When the glycogen reservoirs are low there is a deposition of glycogen.

It was found that, if the glycogen reservoirs of the body were moderately filled, the respiratory quotient of the pabulum retained

in the body after giving meat in excess was often 0.85 and indicated the deposition of both carbohydrate and fat in animal's body, both derived from the metabolism of protein.

The amount of C retained as fat or carbohydrate bore no relation to the height of the heat production, so *the specific dynamic action of protein cannot be due to the deposition of synthetically formed glycogen or fat* (see p. 397).

It is quite possible that the origin of fat from protein is in its nature the same as the origin of fat from carbohydrates.

In the first edition of this work (1906, p. 123) it was computed from the investigations of Cremer with the cat and from those of Rubner with a dog that 40 per cent. of the protein carbon which was capable of conversion into glucose could be retained in the organism either as glucose or as fat. This is to be compared with 33 per cent. of such glucose retention indirectly measured by Williams, Riche, and Lusk and 50 per cent. of such potential glucose retained and deposited in the form of fat as measured by Atkinson, Rapport and Lusk.

An interesting contribution to the subject of the possible formation of fat from protein has been made by Weinland,[1] who found in the case of the blow-fly (*calliphora*), which lays its eggs in meat, that both the larvæ and a pulp made by crushing them had the power, in the absence of oxygen, to split peptone into amino-acids, deaminize these with evolution of ammonia, and then with evolution of carbon dioxid to produce higher fatty acids, presumably through synthetic union of fragments of the acids which had been freed of their amino groups. Such a procedure reasonably explains the formation of fat from protein in the sense of the older theories (see p. 206).

THE question of a "fatty degeneration" of protein under pathologic conditions is another matter and will be considered in another place. (See Chapter XXVI.)

[1] Weinland, E.: Z. f. Biol., 1908, **51**, 197.

CHAPTER XII

THE INFLUENCE OF PROTEIN FOOD (Concluded)

PART IV—ITS SPECIFIC DYNAMIC ACTION

I maintain this as an incontestible fact. It is of itself so important that I question whether it is desirable to add a word of explanation. The results of a properly conducted and properly appreciated experiment can never be annulled, whereas a theory can change with the progress of science.—Carl von Voit.

The experiments already described bring to light a very striking change in the metabolism after the ingestion of protein in excess. The total heat production is markedly increased. To what may this be due?

Von Mering and Zuntz[1] believed that such increased metabolism was due to the activity of the intestinal tract after the ingestion of food.

Voit[2] criticised this view, and said that a rise in the carbon dioxid excretion from 366 grams in starvation to 783 grams after ingestion of 2500 grams of meat by a dog (see p. 189) was too great to be due to intestinal activity, and, indeed, corresponded to the rise noted only after the hardest exercise. Furthermore, Voit had shown that after giving a medium quantity of fat, the carbon dioxid excretion and oxygen absorption were almost the same as in hunger, notwithstanding the activity of the filled intestine.[3]

This question has received very painstaking and elaborate investigation at the hands of Rubner, who has published his results in a book entitled "Die Gesetze des Energieverbrauchs bei der Ernährung." This volume is an extension of a work of which a preliminary communication was published by Rubner[4] from Voit's Munich laboratory in 1885.

Rubner shows that bones given to a dog will not increase his metabolism in spite of the intestinal irritation, so the increase after

[1] von Mering, J. and Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1877, **15**, 634.
[2] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Part 1, p. 209.
[3] Compare also Benedict, F. G., and Pratt, J. H.: J. Biol. Chem., 1913, **15**, 1.
[4] Rubner, M.: "Sitzungsber. kgl. bayr. Acad. d. Wissenschaft," 1885, Heft 4.

meat ingestion is not due to a nerve reflex of mechanical nature. Further, the metabolism is not raised after the ingestion of meat extract, so the chemical stimulus of flavors which start activity in the glands does not affect total metabolism. Again, the ingestion of water in the quantity contained in meat, while it may cause a rise in nitrogen in the urine followed by a fall—the rise being due to a rapid washing out of nitrogenous decomposition products—does not alter the total metabolism in any way.

Lusk[1] has shown that urea when given in the quantity which would be liberated from considerable amounts of meat, and sodium chlorid, the ingestion of which might induce osmotic exchanges in the cells, have no effect upon the heat production.

Benedict and Emmes[2] have demonstrated that cathartics and agar-agar, when given to man, have no effect upon total heat production despite the intestinal activity which they produce.

The absence of true "intestinal work" or "Darmarbeit" in the sense of Zuntz is further shown by the fact that Johansson[3] has given a fasting man 75 grams of glucose without the slightest increase in the output of carbon dioxid. If glucose had been consumed the carbon dioxid excretion would have risen (see p. 375), therefore glucose was retained as glycogen. Since all these processes were without effect on the carbon dioxid output, it followed that the intestinal activities involved did not cause an increase in the total metabolism. Of similar import are the results by the same writer after administering 50 grams of glucose to a diabetic. The sugar was absorbed and eliminated in the urine without affecting the carbon dioxid output.

The increase in metabolism is greater in the case of protein than with any other food-stuff. Rubner calls this action of abundant protein food in raising the metabolism the *specific dynamic* action of protein. Rubner found that when dogs were fed with meat their bodies metabolized in largely increased measure without doing any external work. A more rapid respiration alone betokened the increased oxidation and the effort of the body to rid itself of excess of heat through physical regulation. The temperature of the dogs scarcely changed, so perfect is the regulatory mechanism for the discharge of heat. Thus in one dog the temperature was 38.16° before

[1] Lusk, G.: J. Biol. Chem., 1912–13, **13**, 27.
[2] Benedict, F. G., and Emmes, L. E.: Am. J. Physiol., 1912, **30**, 197.
[3] Johansson, J. E.: Skan. Arch. Physiol., 1909, **21**, 1.

the meal, 38.74° during the digestion, and 38.17° at the end of digestion.

If a large quantity of protein be ingested day after day, then the usual specific dynamic action occurs and also a continued "secondary" rise in total day-to-day metabolism, which increases with the continual increase in protein metabolism. When nitrogen equilibrium is established the heat production remains constant at a higher level.

Rubner[1] illustrates this important fact in the following experiment on a dog, the food of which contained 17 grams of nitrogen:

Calories in Meat Ingested	N to Body Gm.	Carbon to Body Gm.	Total Calories of Metabolism
0	−1.31	....	310.61
0	−1.52	....	278.00
481.5	3.95	2.97	311.43
481.5	2.80	3.70	333.82
481.5	2.30	1.61	368.41
481.5	2.20	2.53	361.70
481.5	0.92	4.45	375.47
481.5	0.20	4.31	395.77
0	−3.70	....	357.20
0	−2.64	....	310.29

This experiment of Rubner shows that the amount of protein carbon retained in the body for the retention of carbohydrate or fat has nothing to do with the intensity of the specific dynamic action. Protein retention is much more readily brought about on a mixed diet containing large quantities of carbohydrates, as will be seen in a subsequent chapter.

Thus far in this book the influence of external temperature upon the course of protein metabolism has not been discussed. Rubner has shown that this is a factor of profound significance. It has already been demonstrated how, through *chemical regulation*, the basal requirement of the body is reflexly increased by increasing cold in the environment. Rubner[2] compared the starving metabolism of a dog at different temperatures with that of the same dog when 100, 200, and 320 grams of meat were ingested. The results are presented as follows in terms of calories produced per kilogram of body weight:

[1] Rubner, M.: "Energiegesetze," 1902, p. 246.
[2] Rubner, M.: *Ibid.*, p. 109.

INFLUENCE OF EXTERNAL TEMPERATURE ON METABOLISM AFTER PROTEIN INGESTION. VALUES IN CALORIES

Temperature	Starvation	100 Gm. Meat or 24 Cal. per Kg.	200 Gm. Meat or 48 Cal. per Kg.	320 Gm. Meat or 81 Cal. per Kg.
7°	86.4	....	77.7	87.9
15°	63.0	....	....	86.6
20°	55.9	55.9	57.9	76.3
25°	54.2	55.5	64.9	
30°	56.2	55.6	63.4	83.0

One hundred grams of meat did not change the metabolism at 20°, 25°, or 30°; 200 grams of meat had no effect at 20° or at 7°, but at 25° and at 30° there was an increase, although the food contained fewer calories than the requirement. With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged. In other words, at a temperature of 30° the specific dynamic action of this amount of protein is capable of increasing the heat production above that of starvation by about 53 per cent., while at 7° there is no change whatever. It is also evident that at a high temperature even a small quantity of protein, such as 200 grams of meat, causes a considerable rise of metabolism.

Rubner gives the metabolism in terms of calories per kilogram after the ingestion of 550 grams of meat or 173.8 calories per kilogram of body weight in a dog, as follows:

Temperature	Starvation	550 Grams Meat	Increase
4.2°	128.1	133.5	4.2 per cent.
14.5°	100.9	110.9	9.9 "
22.1°	70.7	101.0	42.9 "
30.7°	62.0	117.2	89.0 "

In certain cases after food ingestion the carbon dioxid excretion may remain constant at different temperatures of environment. This action is seen in the dog mentioned on this page after he had eaten 320 grams of meat at various room temperatures. The increase in body metabolism due to the stimulus of cold (chemical regulation) is not necessary, since heat in excess of the requirement is already available. All that is needed is the arrangement of avenues of escape for the excess of heat produced from the food ingested (physical regulation). This physical regulation is brought about by the evaporation of water and by a change in the distribution of the blood.

How the increased evaporation of water enters as a refrigerating factor is beautifully shown in the experiment on the dog (p. 279) which fasted and then received 100, 200, and 320 grams of meat at various room temperatures. The distribution of the loss of heat by radiation and conduction and by the evaporation of water was as follows:

DISTRIBUTION OF HEAT LOSS FROM A DOG AFTER MEAT INGESTION

Temperature	Hunger		100 Grams Meat		200 Grams Meat		320 Grams Meat	
	Cal. from Radiation and Conduction	Cal. from Evaporation of Water	Cal. from Radiation and Conduction	Cal. from Evaporation of Water	Cal. from Radiation and Conduction	Cal. from Evaporation of Water	Cal. from Radiation and Conduction	Cal. from Evaporation of Water
7°	78.5	7.9	....	....	67.1	10.6	78.5	9.4
15°	55.3	7.7	....	....	46.7	11.2	76.2	10.4
20°	45.3	10.6	46.7	9.2	49.5	15.4	....	....
25°	41.0	13.2	....	....	....	....	....	....
30°	33.2	23.0	34.1	21.5	27.8	35.6	34.5	48.5

It is evident from the above that the greater part of the loss of heat at a low temperature was by radiation and conduction, but at a high temperature (30°) the loss by the evaporation of water was largely increased. The extra heat production on account of the specific dynamic action of the protein was lost through the increased evaporation of water. Much meat on a hot day would, therefore, seem contraindicated.

While the chemical regulation protects the body from an abnormal fall in temperature, the physical regulation prevents an abnormal rise in temperature. The organism may be at times under the influence of one means of regulation, at times of the other, and without being conscious of any difference. Cold-blooded animals have inadequate chemical regulation, and their temperature falls with that of their surroundings (see p. 118).

A study of the specific dynamic action of protein in its relation to temperature changes gave Rubner[1] new points of view. He saw (experiment on p. 279) that by chemical regulation the metabolism in a fasting dog was increased from 54 to 86 calories per kilogram, an increment of 32. And he likewise observed that after the ingestion of 320 grams of meat the heat produced at a room temperature of 30° rose from 56 in starvation to 83, a difference of 27 calories. The

[1] Rubner, M.: "Energiegesetze," p. 145.

source of the increase through chemical regulation is known to be chiefly in the muscles. The increase brought about by protein ingestion had been shown by Rubner to be due not to any such thing as intestinal activity (see p. 276), but rather to some specific heat-raising effect of protein metabolism itself. It was apparent that these two sources of increased heat might enter into a reciprocal arrangement, because on cooling the atmosphere in which the dog lived to 7° C. the metabolism, after the ingestion of 320 grams of meat, remained at 87.9 calories in contrast with 83.0 on feeding at 30°. Here the heat due to the specific dynamic action was used in replacement of that induced by chemical regulation. This illustrates Rubner's modified idea of his *compensation theory*, or a reciprocity between heat produced in the muscles by chemical regulation and the extra heat production brought about through the ingestion of food.

Since the extra heat production after food ingestion could be utilized instead of heat from chemical regulation, Rubner perceived that the true increase through specific dynamic action could be measured best at the temperature of 33°, where there was no reflex increase in metabolism through chemical regulation.

It was especially important to make experiments regarding the action of food-stuffs at a temperature of 33°, for that is the temperature with which man surrounds his skin. By means of clothes and artificial heating man constantly tries to remove himself from the influence of chemical regulation. His daily life is practically under the influence of a tropical climate. His metabolism is unchanged from the normal when he is immersed in a bath at 33°.[1]

Rubner, therefore, planned an experiment in which a dog was kept at a temperature of 33°. At times the animal was made to fast in order that the basal requirement could be determined, and during other definite periods meat, fat, and carbohydrates, either alone or combined, were ingested, and the increased metabolism due to the varying dietaries was noticed. The experiment extended over a period of forty-six days.

A summary of the results obtained is graphically illustrated by the accompanying Fig. 17, which has been taken from Rubner.[2]

It appeared evident that meat ingestion raised the metabolism most, fat next, and sugar least of all the food-stuffs. The ingestion

[1] Rubner, M.: Arch. f. Hyg., 1903, **46**, 390.
[2] Rubner, M.: "Energiegesetze," p. 322.

of the starvation requirement for energy in the form of fat raised the metabolism 12.7 per cent.; in the form of sugar, 5.8 per cent. During the two periods, when approximately 100 per cent. of the basal requirement was ingested as meat, there was an *average increase* in the metabolism of 36.7 per cent.

After making deductions for the effect of the fat contained in the meat given, Rubner computed that there was an average increase in metabolism of 30.94 calories for 100 calories contained in the protein

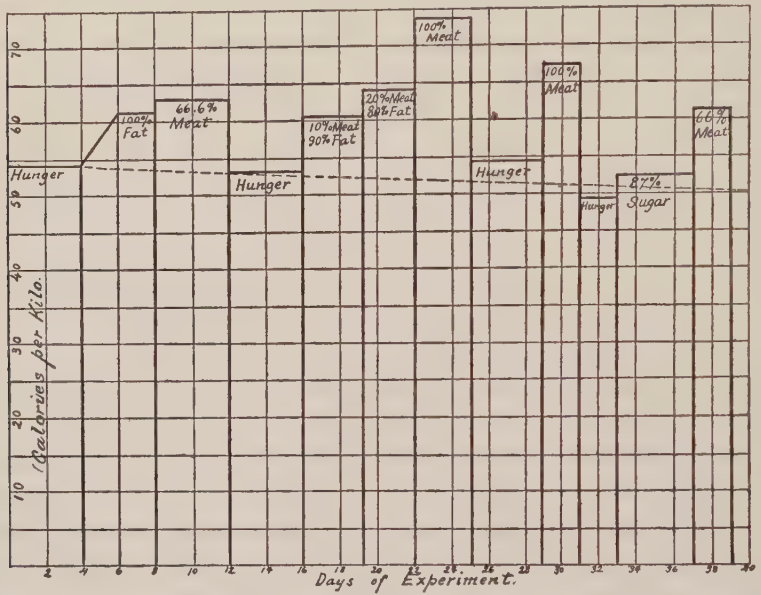


Fig. 17.—Rubner's chart indicating the specific dynamic action of different foodstuffs ingested at a room temperature of 33°. The dotted line indicates the height of the fasting metabolism.

of the diet in the resting animal when it was outside of the influence of the chemical regulation of temperature. The action of gelatin was similar, the increase in metabolism being 28 per cent. for every 100 calories in the gelatin ingested.

Again Rubner[1] has determined the amount of the metabolism of a fasting dog and that of the same dog made diabetic with phlorhizin (see p. 673). Under the latter circumstances the protein metabolism is greatly increased. He found that for every 100 calories increase in body protein broken down there was an increased heat production of 31.9 calories. Here was a rise in heat production not due to protein

[1] Rubner, M.: "Energiegesetze," p. 370.

ingestion and, therefore, not due to intestinal work, but due to the mere fact of increased protein metabolism in starvation. The specific dynamic action of protein then may thus be tabulated:

INCREASED HEAT PRODUCTION FOR EVERY 100 CALORIES INGESTED OR METABOLIZED

Meat protein	30.9
Gelatin	28.0
Body protein (phlorhizin diabetes)	31.9

The Rubner values for the specific dynamic action of the different food-stuffs are the earliest on record. They should not be considered as infallible, though they are frequently so quoted. They are based on experimental periods of 24 hours, and no account was taken of the muscular movements of the dog.

If I take the values found in my laboratory and calculate them according to Rubner I find

100 cals. ingested as protein of meat	increase heat production	30	cals.	(1).
100 " " " fat	" " "	4.1	"	(2).
100 " " " glucose	" " "	4.9	"	(3).

These results were all obtained with dogs which were in complete repose.

Williams, Riche, and Lusk employed another method for estimating the specific dynamic action of protein, based on the following arguments: (1) The protein *ingested* may or may not be metabolized, and protein *deposited* is believed by Rubner to exert no specific dynamic action. (2) Part of the protein ingested merely replaces the normal "wear and tear" protein metabolism of the tissues, the amino-acid content of which may always be operating to increase mildly the basal metabolism. If these facts are true, then the extra protein metabolized should be the factor to be compared with the heat production of the specific dynamic action. Thus calculated, one arrives at the following relations:

Food	Every Extra 100 Cals. Contained in Protein Metabolized Increases the Heat Production in Calories
1200 gm. meat	45
700 " "	48

Since Lusk has shown that 52 per cent. of the calories in protein may pass through the glucose stage, these results, standing by them-

[1] Williams, H. B., Riche, J. A., and Lusk, G.: J. Biol. Chem., 1912, **12**, 371.
[2] Murlin, J. R., and Lusk, G.: *Ibid.*, 1915, **22**, 15.
[3] Lusk, G.: *Ibid.*, 1912–13, **13**, 27.

selves alone, would afford an interesting confirmation of Rubner's theory that the specific dynamic action of protein is due to the oxidation of those fragments of protein which are not convertible into glucose (see p. 670).

In man the specific dynamic action of meat, calculated after the fashion above, is greater than in the dog. Williams, Riche, and Lusk recalculated the values given by Gigon,[1] obtained by him after giving casein to men, and to these items may be added the calculations of Aub and Du Bois[2] upon subjects investigated by them.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN MAN

Subject	Food	Body Weight	Every Extra 100 Cals. Contained in Protein Metabolized Increases the Heat Production in Calories
	Gm.	Kg.	
Normal man	Casein, 50 gm.	....	67
	" 100 "	....	56
	" 150 "	....	83
	" 200 "	....	74
Normal man (W. B.)	Meat 600 "	....	82
Normal man (S. K.)	" 660 "	49.5	76
Legless man (H. J.)	" 660 "	55.0	77
Achondroplasia (R. de P.)	" 662 "	41	71

In these last mentioned human subjects, not only was the basal metabolism proportional to the surface area, but the specific dynamic action of protein was very similar in a dwarf and a legless man with reduced muscle tissue to that found in normal men. The results of Aub and Du Bois are shown in Fig. 18.

In the achondroplastic dwarf the maximal increase in the production of heat was 46 per cent., contrasting with 90 per cent. in the dog. It is probable that the difference is due to a difference in the capacity for rapid absorption of amino-acids from the intestine. The sulphur elimination as usual is more rapid than that of the nitrogen.

Rapport,[3] extending Rubner's work, finds that the specific dynamic action of such various proteins as those contained in beef, casein, gliadin, codfish, chicken, and gelatin, when given to a dog in

[1] Gigon, A.: Pflüger's Arch. gesam. Physiol., 1911, **140**, 544.
[2] Aub, J. C., and Du Bois, E. F.: Arch. Int. Med., 1917, **19**, 840.
[3] Rapport, D.: J. Biol. Chem., 1924, **60**, 497.

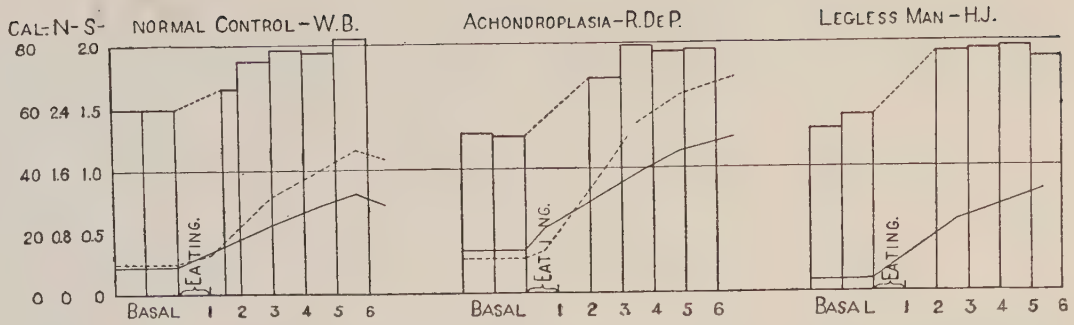


Fig. 18.—Illustrating the specific dynamic action of protein in man. The columns show the basal heat production in calories per hour rising after the subject has eaten meat containing 23 to 25 gm. of nitrogen. The dotted line represents the excretion of sulphur in the urine in decigrams, the continued line, the nitrogen elimination in grams per hour (Aub and DuBois). (Reproduced by permission from E. F. DuBois' "Basal Metabolism in Health and Disease," Lea & Febiger, Philadelphia, 2d ed., 1927, p. 33.)

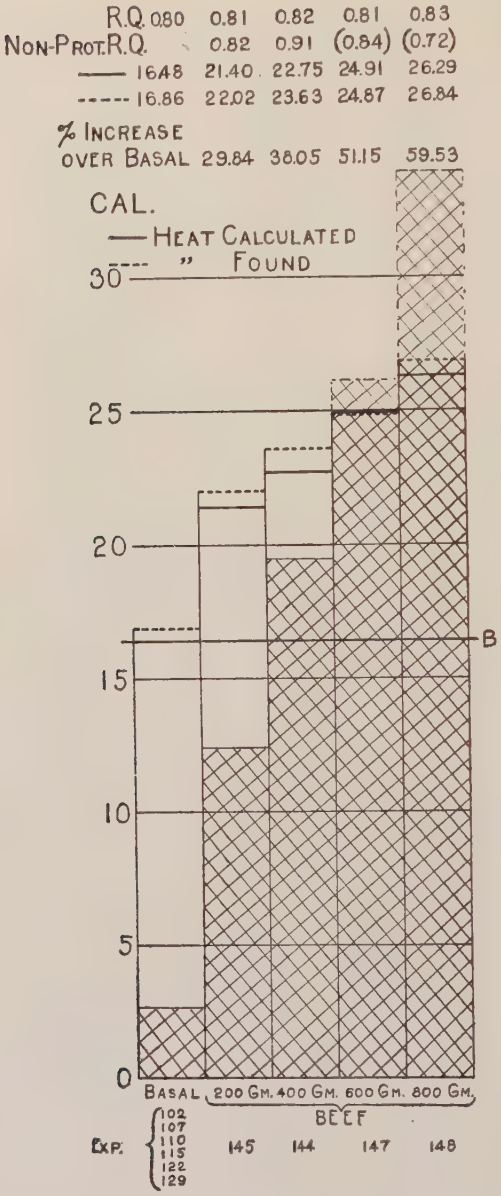


Fig. 19.—The rise in heat production after giving 200, 400, 600, and 800 gm. of beef. The cross lined spaces represent protein metabolized. (Weiss and Rapport.)

amounts containing 6 gm. of nitrogen, is the same. This appears in the following table:

AVERAGE INCREASES IN METABOLISM IN A DOG, PER HOUR OF A 4-HOUR PERIOD, FOLLOWING THE INGESTION OF PROTEINS CONTAINING 6 GM. N

	Calories Indirect	Increase over the Basal
		Per Cent.
Beef, 200 gm.	22.1	34
Casein, 43.67 gm.	21.5	31
Gliadin, 37.5 gm.	22.3	35
Codfish, 218.2 gm.	22.2	35
Chicken, 157.1 gm.	21.6	31
Gelatin, 38.7 gm.	21.3	29.3
Gelatin, 38.7 gm., + cystin, 1 gm.	21.4	29.7
Beef + casein (½ portions of each)	21.8	32

That the ingestion of meat in increasing quantities increases the heat production is shown in the diagram of Weiss and Rapport,[1] here reproduced (Fig. 19).

It will be observed that after giving 800 gm. of meat the retained moiety has a respiratory quotient of 0.72, thus confirming earlier work which showed that fat formed from protein may be deposited (see p. 273).

It has furthermore been shown by Falta, Grote, and Staehelin[2] that casein and the amino-acids resulting from the hydrolysis of casein when given to a dog exert the same specific dynamic action as do the proteins of meat.

THE CAUSE OF THE SPECIFIC DYNAMIC ACTION OF PROTEIN

In 1881 Voit laid down the principle that the intensity of metabolism in the cells was modified by the quality and quantity of the food materials brought to them by the blood. He believed that the inherent power of the cells to metabolize was augmented by the presence of increased quantities of food-stuffs. Rubner developed another conception. He declared that the fundamental metabolism of a normal warm-blooded animal was always constant, and that the effect of food ingestion did not change this. The increased heat production which followed the taking of food was due to heat devel-

[1] Weiss, R., and Rapport, D.: J. Biol. Chem., 1924, **60**, 513.

[2] Falta, W., Grote, F., and Staehelin, R.: Hofmeister's Beitr. chem. Physiol. u. Path., 1907, **9**, 334.

oped from a lot of intermediary reactions and oxidations, and had nothing whatever to do with the fundamental level of the cellular requirement of energy which was entirely unchanged. Thus, when protein was metabolized it could supply energy for the maintenance of true cellular activity in so far as glucose was produced from it, whereas other intermediary cleavage products were simply oxidized with the production of extra heat, which was in no way involved in the life processes of the cells. The utilization of energy in protein might be compared with the burning of a tree as fuel for the steam engine, the trunk of the tree being used as fuel within the engine for the production of power, whereas the limbs and twigs are burned as brush outside and supply only heat.

The theory may be schematically indicated as follows:

STARVATION REQUIREMENT OF POTENTIAL ENERGY BY CELLS = 100 CALORIES

140 Calories in Protein of Meat Ingested

40 Calories = free heat liberated in early cleavage, available in replacement of heat of chemical regulation.

100 Calories = Potential energy from protein available for cell life.

This conception was founded on the erroneous idea that sugar exerted little or no specific dynamic action (see p. 381).

Experiments were instituted in the author's laboratory[1] with the intention of more fully establishing the truth of Rubner's theories of specific dynamic action.[2] It was known that glycin and alanin were completely convertible into glucose in the diabetic organism, whereas glutamic acid was in part so converted, three of its five carbon atoms passing into glucose, the other two being oxidized. It follows from Rubner's hypothesis that glycin and alanin should exert no specific dynamic action, whereas glutamic acid should manifest this phenomenon. The reverse proved to be true: glycin and alanin are capable of greatly increasing the heat production, whereas the strong dibasic glutamic acid is without influence. Glycin (glycocoll) and alanin produce powerful effects, lasting eight and five hours respectively, whereas on giving those quantities of glucose into which the amino-acids are convertible only an almost negligible influence is observable.

[1] Lusk, G.: J. Biol. Chem., 1912–13, **13**, 155.
[2] The argument here presented is to be found in Lusk, G.: *Ibid.*, 1915, **20**, p. viii.

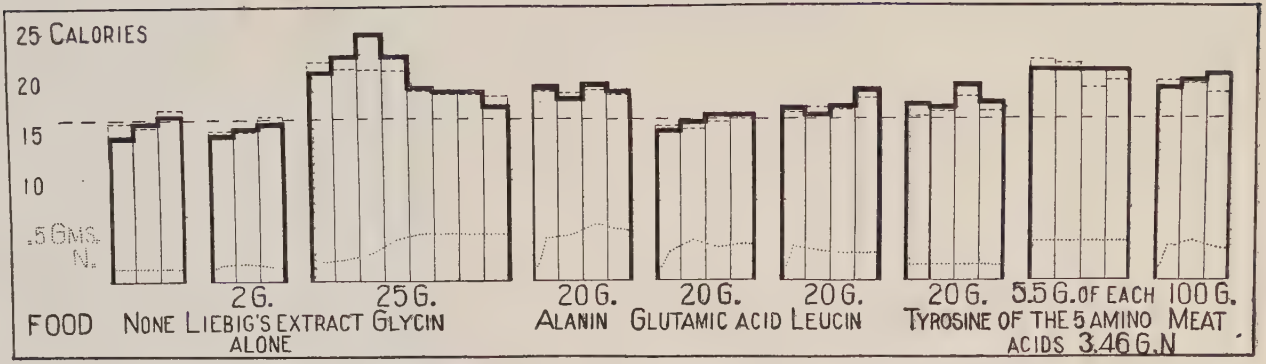


Fig. 20.—Dog II. Hourly metabolism beginning the second hour after giving amino-acids with Liebig's extract. Heavy line ———— calories calculated. Broken line - - - - - - - calories found. Dotted line ..... nitrogen of protein plus amino-acid eliminated.

These facts are brought out in Fig. 20. It should be remembered that 25 grams of glycin and 20 grams of alanin are each convertible into 20 grams of glucose. Leucin and tyrosin exerted only a slight effect upon the heat production. A mixture of 5.5 grams each of glycin, alanin, glutamic acid, and tyrosin, containing 3.46 grams of nitrogen, produced about the same specific dynamic action as 100 grams of meat which contain about 3 grams of nitrogen.

It is important to realize the *constancy of the specific dynamic action.* The dog, the constancy of whose basal metabolism has already been described (see p. 171), reacted in the following manner after receiving 10 gm. glycin[1] at intervals of a year apart:

Date	Food	Metabolism per Hr.		
		Basal	After Glycin	Increase
	Gm.	Cals.	Cals.	Per Cent.
Mar. 21, 1923.....	Glycin, 10	16.48	19.98	21 2
Dec. 10, 1923.....	" 10	16.48	19.91	21.4
Mar. 7, 1924.....	" 10	16.48	20.05	21.7
			19.98	21.4

The values given are for the averages of the 2d, 3d, and 4th hours after giving glycin.

Not only this, but if two dogs have the same weight and the same basal metabolism they will show the same increase in heat production when given 10 gm. of glycin. This has been pointed out by Rapport,[2] who compared the results he obtained with a dog at Cleveland, Ohio, with those obtained by Plummer, Deuel, and Lusk,[3] who worked in New York.

	Food	Wt.	Metabolism per Hr.	
			Basal	Increase
	Gm.	Kg.	Cals.	Per Cent.
Rapport's dog.....	Glycin, 10	6.5	12.4	29
Plummer, Deuel, and Lusk's dog.....	" 10	6.7	13.0	28

[1] Weiss, R., and Rapport, D.: J. Biol. Chem., 1924, **60,** 513.
[2] Rapport, D.: *Ibid.*, 1926–27, **71,** 75.
[3] Plummer, N. H., Deuel, H. J., Jr., and Lusk, G.: *Ibid.*, 1926, **69,** 339.

Weiss and Rapport showed further that if gelatin or casein be administered to a dog the specific dynamic action is a constant factor. This appears in the following table:

Date	Food	Metabolism per Hr.		
		Basal	After Gelatin	Increase
		Cals.	Cals.	Per Cent.
Feb. 9, 1923.....	Gelatin (6 gm. N)	16.48	21.19	28.6
Apr. 30, 1923.....	" 6 "	16.48	21.41	29.9
Dec. 7, 1923.....	" 6 "	16.48	21.62	31.2
Mar. 18, 1924.....	" 6 "	16.48	21.01	27.5
		16.48	21.31	29.3

These reactions led Lusk[1] to say: "The heat produced by mixing a given quantity of water and sulphuric acid together in a test-tube is scarcely more exactly measurable than are these reactions of living cells to the amino-acids or polypeptids which reach them after meat or kindred substances are taken as food."

In order to understand the method of investigating the specific dynamic action it is necessary to regard the dog in the light of a test-tube. The results outlined above could not have been obtained without orderly reactions being present. In other words, ammonia split from glycin or from protein is not able to make alanin over and over again a variable and indeterminate number of times, in the sense of Knoop (see p. 220), for each time it was formed it would exert its well-known specific dynamic action, and the heat production would be proportionate to the number of the reactions which took place.

Returning now to the question of the individual amino-acids, it may be affirmed on the basis of the work of Atkinson and Lusk[2] that *aspartic acid*, like glutamic acid, exerts no specific dynamic action, nor does *asparagin* $NH_2—CO—CH_2—CHNH_2—COOH$. Asparagin, containing the same percentage quantity of nitrogen as glycin, has no effect on the heat production. The specific dynamic action therefore is not proportional to the amino-acid groups in the molecule. *Succinic acid*, a possible intermediate of glutamic acid, has no influence on metabolism.

[1] Lusk, G.: Chapter on "Problems of Metabolism," Mayo Foundation "Lectures on Nutrition," Philadelphia and London, 1925, p. 70.

[2] Atkinson, H. V., and Lusk, G.: J. Biol. Chem., 1918, **36**, 415.

Recently Rapport and Beard[1] have made some very important additions to our knowledge. They confirm the work which shows that leucin has only a small specific dynamic action, they find that tyrosin has a greater specific dynamic effect than found in the earlier experiments, and they discover that *phenylalanin has a greater specific dynamic action than any amino-acid.* This deals a blow to the conception that the specific dynamic action is due to the NH_2 group.

Their results after giving 10 gm. of various amino-acids to their small dog may thus be written:

Amino-acid	Amount Ingested	Increase over Basal Metabolism
	Gm.	Per Cent.
Glycin	10	29
Alanin	10	20
Leucin	10	10
Phenylalanin	10	39
Tyrosin	10	20

Also, it may be added that Plummer, Deuel, and Lusk found the same specific dynamic action with glycyl-glycin[2] as after giving glycin.

The specific dynamic action of amino-acids intravenously injected has been made the subject of several studies. Seth and Luck[3] injected a dog weighing 10 kg. intravenously with 1 gm. of glycin and witnessed its rapid withdrawal from the blood by the tissues, and a slow formation of urea which followed much later.

GLYCIN, 1 GM. INTRAVENOUSLY. DOG, 10 KG.

Period	N in 100 C.C. Blood	
	Amino N	Urea N
	Mg.	Mg.
Before injection	5.9	7.7
2 min. after injection	10.0	7.9
8 " " "	8.4	7.8
17 " " "	6.7	8.7
28 " " "	6.5	8.2
57 " " "	5.8	7.6
94 " " "	5.9	8.3

Weiss and Rapport[4] administered 10 gm. of glycin *per os*, intravenously, and subcutaneously, and determined the average heat

[1] Rapport, D., and Beard, H. H.: J. Biol. Chem., 1927, **73**, 299.
[2] A present from Prof. Max. Cremer, of Berlin.
[3] Seth, T. N., and Luck, J. M.: Biochem. J., 1925, **19**, 366.
[4] Weiss, R., and Rapport, D.: J. Biol. Chem., 1924, **60**, 513.

production of the 2d to the 5th hours, *i.e.*, those of the high metabolism. The work may be summarized as follows:

Food	Increase above Basal Metabolism Per Cent.
Glycin, 10 gm. *per os*	21
Glycin, 10 gm. intravenously	19
Glycin, 10 gm. subcutaneously	15

Little difference is to be observed.

Liebeschütz-Plaut[1] denies that intravenous injection of glycin increases the metabolism. Guttmacher and Weiss[2] point out that under light urethan narcosis the specific dynamic action of glucose and glycin is present in rabbits but is abolished in deep narcosis. This probably explains Frau Liebeschütz-Plaut's results, for Aub, Everett, and Fine[3] show that cats under urethan or paraldehyd anesthesia show no specific dynamic reaction to intravenously injected glycin, whereas 5 gm. of glycin, given intravenously to decerebrate cats, shows a powerful action. Glutamic acid thus injected is without effect. Mann, Wilhelmj, and Bollman[4] confirm the observations that intravenous injections of glycin and alanin in normal dogs result in an increase in heat production.

Guttmacher and Weiss think it possible that decreased irritability and reaction of body cells underlies the abolition of the specific dynamic action in deep narcosis, but they offer another solution of the problem.

"We believe that our experiments show that the nervous system plays an essential rôle in the problem. We hardly can withstand the temptation of postulating a center somewhere in the medulla to which chemical stimuli are brought and which in turn sends efferent impulses to stimulate individual organ groups to increased metabolism."

Rapport and Katz,[5] on the other hand, have studied oxygen absorption of muscles in an isolated hind leg of a dog perfused with blood from another dog and then have added glycin to the perfusate. Without glycin the oxygen consumption of the muscle fell 40 per cent. in three hours; in the presence of glycin it rose 55 per cent. in

[1] Liebeschütz-Plaut, R., and Schadow, H.: Pflüger's Arch. gesam. Physiol., 1926, **214**, 537.
[2] Guttmacher, M. S., and Weiss, R.: J. Biol. Chem., 1927, **72**, 283.
[3] Aub, J. C., Everett, M. R., and Fine, J.: Am. J. Physiol., 1926–27, **79**, 559.
[4] Mann, F. C., Wilhelmj, C. M., and Bollman, J. L.: *Ibid.*, 1927, **81**, 496.
[5] Rapport, D., and Katz, L. N.: *Ibid.*, 1927, **80**, 185.

the 3d hour. The authors conclude "Glycin acts as a powerful stimulator of the cell metabolism in an isolated perfused group of muscles" and that its specific dynamic action "is a direct effect upon the cells of the tissues stimulated, and that no central control outside of the tissue need be postulated."

Since the liver is the organ for the deamination and glucose synthesis of amino-acids, it is important to know whether it is also the site of the specific dynamic action. Aub and Means[1] find that both the basal metabolism and the specific dynamic action are in every way normal in twelve cases of liver disease. Cases of cirrhosis showed the highest metabolic response to protein catabolism. They conclude that the specific dynamic action of protein does not have the liver as its site, or that the liver can perform this function even in disease. Mann,[2] however, states that thus far he has been unable to obtain any specific dynamic action in dehepatized dogs. If this be true, it is hard to reconcile with the results of Rapport and Katz.

The curve of nitrogen elimination shown in Fig. 20 does not truly represent the rapidity of the metabolism of the amino-acids. If instead of using the hourly extra nitrogen elimination after giving glycin or alanin one employs the "extra glucose" elimination after giving these substances to a dog with phlorhizin glycosuria, it is discovered that the maximum breakdown of the amino-acid takes place during the second hour after their ingestion. The accompanying chart (Fig. 21) shows such experiments as accomplished by Csonka.[3]

This chart shows that the rapidity of the absorption and elimination of glucose ingested in phlorhizin glycosuria is almost the same as the rapidity of the absorption, deamination, synthetic sugar production, and the elimination of such sugar after the administration of an iso-glucogenic quantity of glycin and a comparable quantity of alanin.

It may be added that Janney[4] reports that after giving meat to a phlorhizinized dog the extra sugar appears in the urine quite as rapidly as after giving glycin or alanin. The rapidity of the attack of digestive enzymes upon protein must, therefore, be much greater than has hitherto been supposed.

Using the results obtained with glycin (glycocoll) and alanin, Lusk[5] found that the hours of the greatest heat production after the

[1] Aub, J. C., and Means, J. H.: Arch. Int. Med., 1921, **28**, 173.
[2] Mann, F. C., Wilhelmj, C. M., and Bollman, J. L.: Am. J. Physiol., 1927, **81**, 496.
[3] Csonka, F. A.: J. Biol. Chem., 1915, **20**, 539.
[4] Janney, N. W.: *Ibid.*, 1915, **22**, 191.
[5] Lusk, G.: *Ibid.*, 1915, **20**, 555.

administration of these substances were coincident with the hours of their greatest metabolism. Also, it was found that the increase in metabolism after giving glycin and alanin together is equal to the sum of the effects produced by either alone, an experiment performed at the suggestion of Professor Rubner when he visited me at my Adirondack camp in 1912. Furthermore, the increase of metabolism after giving 20 grams of glycin is twice as great as after taking 10 grams.

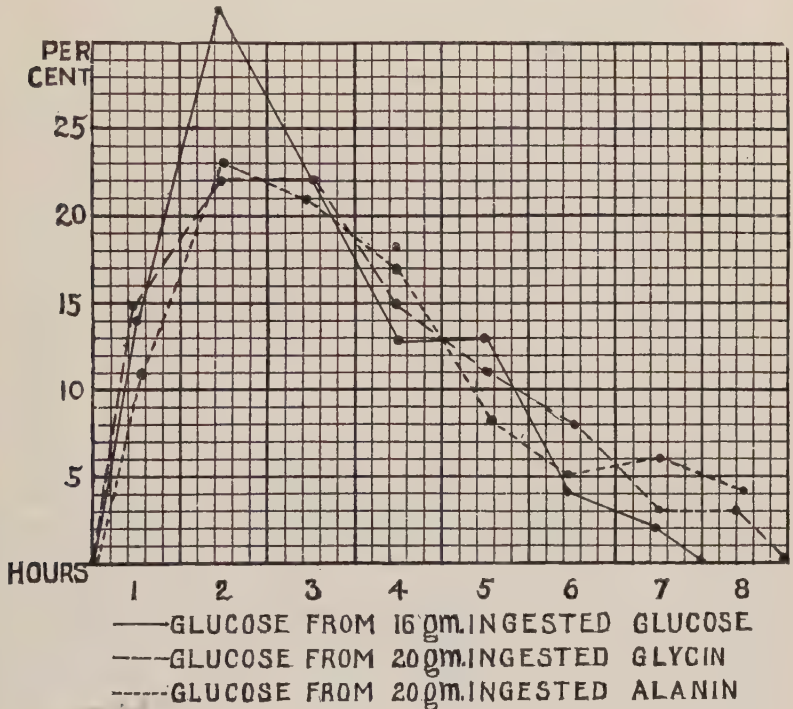


Fig. 21

Similar relations obtain after different quantities of alanin. This accords with Rubner's discovery that the intensity of the specific dynamic action is proportional to the quantity of protein ingested. When one compares the heat-increasing power of glycin and alanin upon metabolism, it is found that this power is not proportional to their respective abilities to form sugar, but rather to the number of molecules of glycollic and lactic acids which they are respectively supposed to yield on deamination.

In one experiment 20 gm. of glycin were given to a dog and the metabolism rose 34 per cent. above the basal level. The 20 gm. of

glycin contained 42 physiologically available calories, of which 34 calories, or 81 per cent, may be estimated from Csonka's values to have been available for metabolism during the 2d to the 7th hours. The actual extra heat production was 33.75 calories, or exactly the quantity estimated as obtainable from the glycin metabolism of the period. The course of inquiry into this phenomenon which naturally suggests itself is whether glycin is without action upon the body-cells; that is, whether it merely explodes and yields heat, or whether it directly stimulates the cells, thereby raising metabolism to a higher level. This point was determined by giving glycin to a phlorhizinized animal. Under these circumstances there is no oxidation of the material ingested and the energy content of the glycin is eliminated in the urine in the form of sugar and urea. The metabolism was largely increased, notwithstanding the fact that there was no oxidation of the ingested material. Exactly the same phenomenon followed the ingestion of alanin in phlorhizin glycosuria. The ingestion of glucose was without effect even after 70 grams had been given. The cause of the specific dynamic action of glycin and alanin therefore lies in a chemical stimulation of the cells, causing them to metabolize more material. This confirms the older view of Voit that the action of food increases the power of the cells to metabolize.

An experiment[1] which shows the effect of giving 20 grams of glycin to a phlorhizinized dog is here reproduced:

DOG III, MARCH 25, 1915, EXPERIMENT 104. BASAL PHLORHIZIN METABOLISM AS AFFECTED BY 20 GRAMS OF GLYCIN IN 210 C.C. OF WATER AT 38° PLUS 1 GRAM OF LIEBIG'S EXTRACT

Hours		R. Q.	Calories	
			Indirect	Direct
1	Basal	0.733	23.78	24.53
2	"	0.716	23.82	23.84
	Average	0.724	23.80	24.18
3	Glycin, 20 grams	0.707	34.21	32.34
4		0.745	31.65	29.47
5		0.700	29.24	30.07
6		0.702	25.99	26.85
7				
	Average	0.720	30.27	29.68

Although glycin was not oxidized, but appeared as glucose and urea in the urine, yet there was the same increase in the heat produc-

[1] Lusk, G.: *Loc. cit.*, p. 612.

tion after its ingestion in phlorhizin glycosuria as when the dog was normal. It is, therefore, evident that the cause of the specific dynamic action of glycin is independent of the oxidation of glycin or the liberation of its energy content.

A closer analysis of this experiment, which was made upon the same dog to which 20 gm. of glycin had been given when it was normal, shows an increase in heat production for 4 hours, beginning at the 2d, of 25.9 calories in diabetes and in the normal condition of 24.5 calories. This is a matter of significance because under the ordinary normal conditions of basal metabolism glucose and fat are being oxidized together, whereas in the diabetic condition fat alone is used to supply the extra heat of the specific dynamic action of glycin. These results were first presented at the International Physiological Congress held in Groningen in 1913,[1] and I spoke of the phenomenon as *amino-acid stimulation*, believing it to be directly active on cellular protoplasm.

The specific dynamic action of glycin was fully confirmed by Grafe,[2] who reports that after giving 50 grams of glycin to a normal dog the oxygen absorption rose 77 per cent., while in man the increase was 14 per cent.

The chemical stimulus does not reside in the amino-acids themselves, for there is no accumulation of amino-acids in the tissues after the ingestion of meat in large quantities. (See Van Slyke, Wishart, p. 86.) Also when protein is deposited in the form of new tissues these amino-acids exert no specific dynamic influence. Rubner[3] gives the following example of the stage of the deposit of protein without a rise in the metabolism of a dog:

	N to Body	Calories per Kg.
Starvation	.....	43.26
Meat	+8.7	44.48

The researches of Hoobler[4] have shown the same to be true of the baby, as appears from the following data:

	Protein Ingested	Protein Destroyed	Protein Added to Body	Calories of Metabolism
	Grams	Grams	Grams	
High protein diet.....	33.1	18.0	15.1	363
High protein diet.....	43.3	18.9	24.4	363

[1] Lusk, G.: Arch. Int. Med., 1913, **12**, 485.
[2] Grafe, E.: Deut. Arch. klin. Med., 1915, **118**, 1.
[3] Rubner, M.: "Energiegesetze," 1902, p. 256.
[4] Hoobler, B. R.: Am. J. Dis. Chil., 1915, **10**, 153.

Such facts demonstrate that the mere absorption of amino-acids and their rebuilding into new protoplasm does not increase the metabolism.

Since the hours of the highest heat production after giving glycin and alanin are the hours of the maximal metabolism of these amino-acids, it seemed likely that the metabolism products, such as glycollic or lactic acids (see pp. 229–231), were indicated as the probable chemical stimuli which act upon the protoplasm of the cells, causing them to oxidize materials in increased measure.

That the chemical stimulus does not act through excitation of the nervous system is to be inferred from the experiments of Tangl,[1] who noticed an increase in the heat production of curarized dogs after giving them protein.

External cold acts reflexly through the nervous system to increase metabolism in a fasting animal and thus prevents a fall in body temperature through the "chemical regulation" of body temperature. According to Rubner's hypothesis, the "free heat" liberated in the intermediary metabolism of protein can be used in lieu of that derived from the increased metabolism induced through the effect of cold.

It may be that the mass action of the various fragments produced in the breakdown of protein in metabolism is also a contributory factor in the higher production of heat, but that it is the main factor is negatived by contrasting the different effect of 20 grams of glutamic acid with that of 20 grams of glycin, the effect of the first being *nil* and that of the latter powerful.

We may now proceed in greater detail into the clouded area of the cause of the specific dynamic action of protein.

THE INTERMEDIARY METABOLISM OF PROTEIN AND THE SPECIFIC DYNAMIC ACTION

Upon the correct interpretation of the behavior of the intermediary metabolites of protein depends the understanding of the cause of the specific dynamic action. Those who have had experience know that perfectly clear theoretical interpretations often vanish in the light of a few new experiments.

One may consider the origin of the specific dynamic action of protein under three different headings: first, is it due to an acid

[1] Tangl, F.: Biochem. Z., 1911, **34**, 1.

stimulus? second, is it due to a coupled reaction of amino-acids with carbohydrate or fat metabolites? third, is it due to intermediate heat-producing oxidations and reductions?

1. *Acid Stimulus.*—Lusk[1] gave 7.6 gm. glycollic acid to a dog and noted that the basal metabolism of 17.6 calories per hour was increased 1.5 calories per hour as measured during two or three hours beginning at the second hour after administration of the substance. The CO_2 combining power of the blood fell from 60 to 40 volumes per cent. and remained at this level for six hours, indicating a very slow combustion of the substance.[2] A like quantity of glycollic acid given as a sodium salt increased the metabolism only 0.9 calorie per hour. On the other hand, 9.5 gm. of glycin neutralized with sodium bicarbonate increased the heat production 5.3 calories per hour for two consecutive hours, an increase which glycin itself would have effected. Sodium bicarbonate, 10 gm., in Liebig's extract of beef when given to the dog was without influence upon the heat production.

Chanutin[3] has shown that the administration of glycin, 15 gm., or alanin, 15 gm., to a dog causes a slight *increase* in the CO_2 combining power of the blood, and the same is true after giving 1000 gm. of meat.

The ingestion of 3 gm. of the easily oxidizable acetic acid increases the metabolism 3.1 calories per hour without changing the CO_2 combining power of the blood, whereas 4.8 gm. of lactic acid, containing more H ions than 3 gm. acetic acid, and reducing the CO_2 combining power of the blood by 14 per cent., raises the heat production 2.7 calories per hour. Lactic acid, 8 gm., given as a sodium salt raises the heat production only 1.4 calories per hour.

Glucose, 58 gm., increased the heat production 5.3 calories per hour for 2 hours without changing the CO_2 combining power of the blood. Lusk called attention to the fact that an amount of glycin containing only 20 physiologically available calories increased the heat production 5.3 calories per hour, whereas 58 gm. of glucose, containing 218 calories, or 11 times as many, raised the metabolism only 4.7 calories per hour. He concluded that, though one might still speak of amino-acid stimulation in the sense that one speaks of the specific dynamic action of protein, one was far from an actual elucidation of what occurs in the cells to produce the phenomenon.

[1] Lusk, G.: J. Biol. Chem., 1921, **49**, 453.
[2] Taistra, S. A.: *Ibid.*, p. 479.
[3] Chanutin, A.: *Ibid.*, p. 485.

One may generalize from the observations above that *the partial replacement of acid for alkali in the circulating blood has little or no influence on the heat production, and that the specific dynamic effect of ingested glycollic and lactic acids is not comparable in intensity to the effect of their corresponding amino-acids, glycin and alanin.* However, this does not exclude the possibility that glycollic or lactic acid, or whatever the first products of deamination may be, may not act as powerful stimuli to the metabolism of the cells if they were liberated at the surface or within the cell as the result of deamination.

2. *A Coupled Reaction.*—Another important theory of the specific dynamic action is that amino-acids act as catalysts in metabolism. On another occasion Lusk[1] wrote the formula for the conversion of glycin into glucose as follows:

$6C_2H_5NO_2$	$+ 3CO_2 + 3H_2O =$	$2C_6H_{12}O_6 +$	$3CH_4N_2O +$	$3O_2$
Glycin		Glucose	Urea	
20 gm.		16 gm.	8 gm.	4.26 gm.
62.2 cals.		60.08 cals.	20.2 cals.	14 cals. (as oxidized fat)
−20.2 cals. of urea				
42. cals. physiologically available.				

The reader will remember that Knoop[2] at the last International Physiological Congress (Stockholm, 1926) advanced the theory that an amino-acid like alanin unites in the body with a fragment of glucose metabolism like pyruvic acid to form acetyl-alanin with the cleavage of CO_2. Acetyl-alanin might then be resolved into its components, alanin and acetic acid. The formula is given on p. 221.

The following analysis is based on the assumptions that (1) glycin unites chemically with pyruvic acid, (2) the total heat derived from pyruvic acid is that potential in glucose its mother substance, (3) the carbon of the glycin is completely convertible into glucose, (4) the carbon in the urea formed is derived from the CO_2 of the blood, (5) the whole of the pyruvic acid is catalyzed into acetic acid and CO_2. On these presumptions the formula becomes:

$6C_2H_5NO_2 + 6C_3H_4O_3 + 3CO_2 + 3H_2O =$	$2C_6H_{12}O_6 + 3CH_4N_2O + 6C_2H_4O_2 + 6CO_2$
Glycin Pyruvic Acid	Glucose Urea Acetic Acid
20 gm. 23.5 gm.	16 gm. 8 gm. 16 gm.
62.2 cal. + 90.3 cal.* =	60.2 cal. + 20.2 cal. + 55.9 cal.
152.5 cal. =	136.3 cal. + 16.2 cal. as free heat.

Values: 1 gm. glycin = 3.11 cal.; 1 gm. glucose, 3.762 cal.; 1 gm. urea, 2.523 cal.; 1 gm. acetic acid = 3.491 cal.

* Heat from original 24 gm. glucose.

[1] Lusk, G.: Med., 1922, I, 346.
[2] Knoop, F., and Oesterlin, H.: Z. physiol. Chem., 1925, 48, 294.

If glycin acts to catalyze pyruvic acid according to the formula above, then of 42.2 calories physiologically available in the organism, 16.3 calories or 40 per cent. in the coupled reaction above might contribute to furnish a part of the specific dynamic action. In the dog the equivalent of 100 per cent. of the physiologically available calories of glycin are liberated to produce its specific dynamic effect.

If glycin catalyzed pyruvic acid so that the quantum of energy contained in the latter were liberated to furnish the specific dynamic action of glycin, then 90 calories would be set free, or more than twice the value known to exist. If the specific dynamic action of glycin were derived from the oxidation of the acetic acid formed in the reaction it would be one and a third times that actually observed.

If acetyl-glycin $CH_3—CO—NHCH_2COOH$, in its transformation into glucose, urea, and acetic acid, requires energy to accomplish the reactions involved, then the 60 per cent. deficit involved in the first explanation of the formula given above might be uncovered. Such details cannot be computed, for the transition products are unknown.

It must be recalled that glutamic acid is convertible into urea and 3 of its C-atoms into glucose, and yet it manifests no specific dynamic action. Also, that the constancy of the specific dynamic action already described would preclude the repetition of a reversible reaction an indefinite number of times. The theory of Knoop is supported by experiments done *in vitro*. Thus Ray[1] found that sodium lactate in solution in an atmosphere of nitrogen is converted into CO_2 and acetaldehyd by H_2O_2. He noted that the reaction was greatly accelerated by the presence of glycin and stated that the oxidation of lactic acid by H_2O_2 was catalyzed by the presence of glycin. He attributed the effect to the presence of the NH_2 group. It may be questioned whether in the organism the urea-forming function does not remove the NH_3 as soon as it is liberated.

Borsook and Wasteneys[2] stated that it was certain that there was an increased oxidability of amino-acids in the presence of glucose, as appears below:

Glycin + ferrous sulphate + H_2O_2 = 8 per cent. NH_3 liberated.
Glycin + ferrous sulphate + H_2O_2 + glucose = 25 per cent. liberated NH_3.

The reaction was accelerated by the presence of phosphates. A glycin compound was formed with glucose or its intermediates which had the ability to reduce methylene blue.

[1] Ray, G. B.: J. Gen. Physiol., 1923–24, **6**, 509.
[2] Borsook, H., and Wasteneys, H.: Biochem. J., 1925, **19**, 1128.

Ort and Bollman,[1] in a more extended series of experiments, find, when glucose solutions are oxidized in the presence of H_2O_2 and in the absence of air, that the reaction is catalyzed by cystin, glycin, alanin, phenyl-alanin, leucin, histidin, and valin. Also that aspartic acid, glutamic acid, and tyrosin are without influence. They associated these results with the specific dynamic action of the several amino-acids.

Perhaps the greatest difficulty of all in accepting the theory that the specific dynamic action of protein rests in the ability of amino-acids to catalyze carbohydrate is that in the fasting phlorhizinized dog, in which the carbohydrate available for oxidation is practically nil, the specific dynamic action of ingested glycin is exactly the same as in the normal animal with ample carbohydrate reserves.

To complete this aspect of the story one must add the important experiments of Witzemann,[2] who finds that glycin, ammonia, glycollic acid, or ammonium glycollate all vigorously catalyze the oxidation of butyric acid in the presence of H_2O_2 in neutral and acid, but not in alkaline solutions. A typical protein like gelatin acts with equal effectiveness. Witzemann concludes that his results suggest that possibly all of the proteins and many of their cleavage products share to a greater or less extent in catalyzing vital oxidation before undergoing oxidation themselves, thus explaining their specific dynamic action.

It is evident that the theoretical enunciation of the cause of the specific dynamic action is full of perplexities.

3. *The Intermediary Heat Production.*—In 1908 Zuntz[3] calculated that the hydrolytic deamination of alanin with the production of lactic acid was accompanied by the absorption of heat, as follows:

		Calories
1 gm. mol. $C_3H_5NH_2O_2$	$= 89 \times 4.372 =$	389.1
less 1 gm. mol. NH_3	$= 17 \times 5.370 =$	91.3
Potential energy of N-free rest.		297.8
1 gm. mol. $C_3H_6O_3$	$= 90 \times 3.661$	329.5
Difference		+31.7

The calories absorbed in the reaction were 8 per cent. of those in the original alanin.

An early calculation made by Meyerhof showed that, when 1 gm. glucose containing 3772 small calories was converted into 1 gm. lactic acid containing 3601 calories, there was a liberation of heat of

[1] Ort, J. M., and Bollman, J. L.: J. Am. Chem. Soc., 1927, **49**, 805.
[2] Witzemann, E. J.: *Ibid.*, p. 987.
[3] Zuntz, N.: Zentralbl. f. Physiol., 1908, **22**, 67.

171 calories +19 calories for heat of neutralization of the lactic acid. The reversible conversion of lactic acid into glucose would therefore involve an energy equivalent of 190 calories or about 5 per cent. of that contained in lactic acid. (A different calculation appears on p. 440.)

I believe that Aubel[1] was the first to publish calculations regarding the heat absorption necessary to convert pyruvic acid, which is formed by oxidative deamination of alanin, into glucose, and gave this as the clue to the secret of the cause of the specific dynamic action of alanin.

Meyerhof[2] quotes a value of 3172.4 calories per gram and 274.5 per mol. for pyruvic acid and gives the following equation for its conversion into glycogen hydrate:

$$\underset{\text{Pyruvic acid}}{2C_3H_4O_3\ \text{aq.}\ (2 \times 274.5\ \text{cal. per mol.})} + 2H_2 = \underset{\text{Glycogen hydrate}}{C_6H_{12}O_6\ (681\ \text{cal.})}$$

To produce glycogen from pyruvic acid requires 142 cal. per mol.

For the oxidative deamination of alanin the following formula represents the relations:

$$\underset{\text{Alanin}}{2C_3H_5NH_2O_2(2 \times 388\ \text{cal.})} + O_2 = \underset{\text{Pyruvic acid}}{2C_3H_4O_3(2 \times 274.5)} + \underset{\text{Ammonia}}{2NH_3(2 \times 91.6)}$$

Thirty-eight calories are therefore required. Adding to this the 142 cal. needed to convert 2 mols pyruvic acid into glycogen hydrate, one obtains 180 calories as the intermediary requirement necessary to change alanin into glycogen. Since the physiological value of alanin 2 mols (alanin 776—NH_3 183) is 593 cals., it appears that $\frac{180}{593}$ or *thirty per cent. of the caloric value of alanin may be required to make these intermediary changes.*

The respiratory metabolism after giving alanin must here be briefly mentioned, though the results obtained are not as satisfactory as those after giving glycin. When alanin is oxidized it has a respiratory quotient of 0.83. When it is converted into glucose by oxidation and reduction it absorbs the equivalent of a molecule of water, and the liberated NH_3 unites with CO_2 of the blood or tissues to form urea. Hence the respiratory quotient obtained after giving alanin to a diabetic dog should fall. Although experiments are on record which are entirely worthy of confidence which show that after giving d-l-alanin to a large diabetic dog nearly the whole amount is converted into glucose, yet, since Csonka's work (see p. 627), it has been customary to assume only a 70 per cent. metabolism of the material. The

[1] Aubel, E.: Bull. Soc. Sc. Hyg. Aliment., 1924, **12**, 257, 416.
[2] Meyerhof, O., Lohmann, K., and Meier, R.: Biochem. Z., 1925, **157**, 459.

amino-acid N increases in the urine, and it is possible that the l-alanin which is foreign to the body is utilized with difficulty.

Upon this basis, 20 gm. of alanin may be calculated as containing 49.8 nutritional calories. Using Csonka's figures for the rapidity of the metabolism of alanin, one may assume that 16, 20, and 16 per cent. of the total transformation of alanin takes place in the 2d and 3d hours after alanin ingestion. This being true, 8, 10, and 8 calories from ingested alanin would be normally derived from its metabolism during these 2d, 3d, and 4th hours.

THE SPECIFIC DYNAMIC ACTION OF 20 AND 30 GM. ALANIN ON DOG III WHEN NORMAL AND OF 20 GM. WHEN DIABETIC WITH PHLORHIZIN

	Calories of Alanin Metabolism Calculated per Hour.	Exp. 43 Normal 20 Gm. Alanin		Exp. 70 Diabetic 20 Gm. Alanin		Calories of Alanin Metabolism Calculated per Hour	Exp. 44 Normal 30 Gm. Alanin	
		R. Q.	Increase over Basal	R. Q.	Increase over Basal		R. Q.	Increase over Basal
2d hour.....	8	0.92	4.8	0.68	1.6	12	0.90	7.1
3d "	10	0.88	4.1	0.66	2.8	15	0.83	8.5
4th "	8	0.87	3.7	0.66	3.6	12	0.83	4.2
	26	....	12.6	....	8.0	39	....	19.8

This analysis shows the following values:

After 20 gm. alanin.
Normal —100 cals. of metabolized alanin increase metabolism 46 cals.
Diabetic—100 " " " " " 33 "
After 30 gm. alanin.
Normal —100 cals. of metabolized alanin increase metabolism 50 "

At the time of the publication of these results by Lusk[1] it was calculated that about 53 per cent. of the caloric content of alanin might reappear as extra heat of the specific dynamic action. The calculations are involved with several possibilities of inaccuracy, but ought to be considered since it is the only material available.

It appears to be fairly an open question whether the heat from the oxidative deamination of alanin and the subsequent requirement of energy for the reduction of pyruvic acid and its conversion into glucose or glycogen is a contributory cause of the specific dynamic action of alanin.

[1] Lusk, G.: J. Biol. Chem., 1915, **20**, 555.

In the table given above there are indications of higher respiratory quotients after giving alanin to a normal dog than those of the normal basal value of 0.85. The same has been noted after giving glycin.[1] It would seem that the extra energy of the specific dynamic action may be readily derived from carbohydrate metabolism. However, in the experiment when alanin was given in diabetes the energy must have been largely, if not exclusively, at the expense of fat. The respiratory quotient is reduced on account of CO_2 withdrawn for urea formation, as stated above. In isolated muscle, when pyruvic acid was being converted into glycogen, Meyerhof reports a respiratory quotient of 2.0, which he says is due to the decarboxylation of pyruvic acid. In the diabetic dog there is no evidence of this. Meyerhof concludes that alanin is not converted into glycogen by the isolated muscle because only the liver possesses the power to deaminize it.

Mann's work, showing that in hepatectomized dogs alanin and glycin have no specific dynamic action, indicates that deamination is necessary for the process, and this takes place in the liver. Here the ammonia which is formed is instantly converted into urea, for the blood is almost free from it (see p. 263). The specific dynamic action is probably due to the behavior of the deaminized remainder. The activity of the amino-acid alanin has just been described; that of glycin is well known, though its intermediary chemistry is elusive. Why phenylalanin should be more potent than either of the above is a mystery.

The hypotheses which have been presented cannot now be welded into a concordant whole. They transcend one's powers to coördinate them. They are mentioned here so that younger workers may realize the bases from which they can approach a fuller understanding of the cause of the specific dynamic action of protein.

VARIOUS ANOMALIES

It has seemed best to refer to three aspects of the specific dynamic action which are not easily explainable.

1. *The Reduction of the Specific Dynamic Action in Disease of the Hypophysis.* The first person to note this was Liebeschütz-Plaut,[2] especially in relation to *dystrophia adiposogenitalis.* She reports that

[1] Plummer, N. H., Deuel, H. J., Jr., and Lusk, G.: J. Biol. Chem., 1926, **69**, 339.

[2] Liebeschütz-Plaut, R.: Deut. Arch. klin. Med., 1922, **139**, 285; Liebeschütz-Plaut, R., and Schadow, H.: *Ibid.*, 1925, **148**, 214.

a lowered specific dynamic action is associated with a smaller rise in the amino-acid content of the blood after meat ingestion than is normally the case. Her work has been confirmed by Liebesny[1] in man and by Foster and Smith[2] on hypophysectomized rats (see p. 612).

2. *The Specific Dynamic Action in Undernutrition is Higher than Normal.*—Mason[3] finds that in the state of undernutrition, in which there is a low level of basal metabolism, the specific dynamic action of all the foods is higher than it is when the person is in a normally nutritive state. McCann[4] found that the specific dynamic action of meat caused the heat production to reach the same height in a man at the end of a week's fast as it did later after a week of normal diet.

Gibbons[5] makes the following interesting comparison between the metabolisms of a fat and a thin dog of equal weights before and after giving 200 gm. of meat.

ON THE SPECIFIC DYNAMIC ACTION OF PROTEINS IN THIN AND FAT INDIVIDUALS (DOGS)

	Weight	Basal Metabolism		Specific Dynamic Action: 200 Gm. Meat 3 to 6 Hrs. after Giving It
		Per Kg.	Per 24 Hrs.	
	Kg.	Cals.	Cals.	Per Cent.
Thin dog (greyhound)	29.30	41.8	1242	14.5
Fat dog (mongrel)	29.30	34.9	1036	9.0

Apparently the thin dog has a constitutionally greater reaction to the specific dynamic action than the fat dog (see p. 318).

3. *The Neutralization of the Effect of Glycin and Alanin When These Are Administered with Protein.* The experiments of Rapport, already described (see p. 287), showed that a great variety of fish, flesh, fowl, and vegetable proteins gave exactly the same specific dynamic action despite their varying content of glycin and alanin, as may be seen below:

Beef	contains	approximately	4	per cent.	glycin	and	8	per cent.	alanin.
Gelatin	"	"	26	"	"	"	9	"	"
Casein	"	"	no		"	"	1.5	"	"
Gliadin	"	"	no		"	"	2.0	"	"

Weiss and Rapport[6] made the surprising discovery that there was no increased specific dynamic action when 10 gm. of glycin or 10 gm.

[1] Liebesny, P.: Biochem. Z., 1924, **144,** 308. Fine literature.
[2] Foster, G. L., and Smith, P. E.: J. Am. Med. Assn., 1926, **87,** 2151.
[3] Mason, E. H.: J. Clin. Invest., 1927, **4,** 353.
[4] McCann, W. S.: Proc. Soc. Exper. Biol. and Med., 1919–20, **17,** 173.
[5] Gibbons, R.: Am. J. Physiol., 1924, **70,** 26.
[6] Weiss, R., and Rapport, D.: J. Biol. Chem., 1924, **60,** 513.

of alanin were added to 40 gm. of either gelatin or casein. The specific dynamic effect of the amino-acids was completely neutralized. The administration of asparagin, which itself has no specific dynamic action, with glycin failed to reduce the activity of the glycin. Furthermore, when glycin was given intravenously and gelatin orally the customary specific dynamic action of glycin was annulled.

Thinking this might be a matter of peptid linkages, Rapport[1] compared the specific dynamic action of gelatin, gelatin acid hydrolysate, and gelatin trypsin hydrolysate and found essentially the same results for all, and a summation of effect when two were given together. But when glycin was added to any one of the substances above mentioned its effect was masked; and the same occurred when glycin was given intravenously and the hydrolysate by mouth.

This was followed by a piece of brilliant analytical work by Rapport and Beard.[2] These authors found the quantity of increased heat production which 10 gm. of five different amino-acids would induce in a dog. They then gave the dog those fractions of casein and gelatin hydrolysates which could be extracted by and precipitated in amyl alcohol. It was found that the specific dynamic action was proportional to that of the several amino-acids contained in Fraction I. This appears in the following table.

THEORETICAL EFFECT OF AMINO-ACIDS CONTAINED IN FRACTION I, COMPARED WITH THE SPECIFIC DYNAMIC ACTION OF THE ENTIRE FRACTION

Amino-acid	Amt. Ingested	Increase over Basal	Gelatin Fraction 5 Gm. N			Casein Fraction 5 Gm. N		
			Amt. in Fraction I		Theoretical Increase over Basal	Amt. in Fraction I		Theoretical Increase over Basal
	Gm.	Per Cent.	Per Cent.	Gm.	Per Cent.	Per Cent.	Gm.	Per Cent.
Glycin	10	29	10.7	3.79	11.0	1.6	0.7	2.0
Alanin	10	20	21.6	7.66	15.3	6.4	2.81	5.6
Leucin	10	10	19.9	7.05	7.1	33.4	14.65	14.7
Phenyl-alanin	10	39	3.9	1.38	5.5	13.4	5.88	23.2
Tyrosin	10	21	Trace	Trace	....	6.9	3.02	6.3
Total					38.9			51.8
Found on administering Fraction I					42.8			53.3

[1] Rapport, D. : J. Biol. Chem., 1926–27, **71**, 75.
[2] Rapport , D., and Beard, H. H.: *Ibid.*, 1927, **73**, 299.

AN INTERPRETATION

Extending their work further Rapport and Beard find that *the specific dynamic action of gelatin and meat may be entirely accounted for by the summated effect of five of their component amino-acids.* Neither casein nor gliadin shows this result, and other active amino-acids are being sought to explain the reason. Their table is as follows:

THEORETICAL EFFECT OF AMINO-ACIDS KNOWN TO HAVE A SPECIFIC DYNAMIC ACTION COMPARED WITH THE EFFECT OF GELATIN, BEEF, AND CASEIN

Amino-acid	Gelatin, 6 Gm. N			Meat, 200 Gm., 6 Gm. N			Casein, 6 Gm. N		
	Amount in Gelatin		Theoretical Increase over Basal	Amount in Meat		Theoretical Increase over Basal	Amount in Casein		Theoretical Increase over Basal
	Per Cent.	Gm.	Per Cent.	Per Cent.	Gm.	Per Cent.	Per Cent.	Gm.	Per Cent.
Glycin	25.5	9.7	29.1	4.0	2.0	6.0	0.45	0.2	0.6
Alanin	8.7	3.3	6.6	8.1	4.1	8.2	1.85	0.8	1.6
Leucin	7.1	2.7	2.7	14.3	7.2	7.2	9.7	3.7	3.7
Phenyl-alanin	1.4	0.5	2.0	4.5	2.3	9.2	3.88	1.7	6.8
Tyrosin	Trace	Trace	....	4.4	2.2	4.4	4.5	2.0	4.0
Total theoretical increase			40.4			35.0			16.7
Found after giving this amount of protein			38.5			33.8			33.3

Out of a search for an explanation of a mystery, *i.e.*, the neutralization of the specific dynamic action of ingested glycin, has come this very valuable contribution, without indeed clearing up the original mystery. For why does glycin ingested with gelatin behave differently from glycin preformed in gelatin? Rubner, in a personal letter to me, suggests that perhaps the cells prefer the natural product to the artificially prepared material. Under these circumstances the ingested glycin would find a different path of destruction from the one it usually followed.

CHAPTER XIII

THE INFLUENCE OF THE INGESTION OF FAT

Investigation of a problem must seek to enlarge the boundaries of knowledge. Mere repetition does not bring progress.—RUBNER.

IN a previous chapter it was shown that the amount of fat in the fasting organism materially affected the amount of protein burned. When there was much fat present little protein was consumed; where there was little fat, much protein burned; and where there was no fat, protein alone yielded the energy necessary for life.

The ingestion of fat alone will not prevent the death of the organism because there is a continual loss of tissue protein from the body, which finally weakens some vital organ to such an extent that death takes place.

In a fasting animal which still contained fat, Voit[1] found that the ingestion of 100, 200, and 300 grams of fat scarcely influenced the protein metabolism. The latter was slightly increased, if anything. Voit's table is as follows:

FAT	UREA	FAT	UREA
0	11.9	300	12.0
0	12.0	0	11.9
100	12.0	0	11.3
200	12.4		

These results have been confirmed by Bartmann,[2] who noted that fat given to the extent of 150 per cent. of the energy requirement was readily absorbed and spared protein to a maximum of 7 per cent. Sometimes when much fat was given there was an increased elimination of nitrogen in the urine, at which time there was also an increased amount of nitrogen in the stools.

To another dog, which in starvation burned 96 grams of fat, Voit gave 100 grams, with the result that it then burned 97 grams. The conditions of the metabolism in these cases were therefore identical. The fat ingested simply burned instead of the body's fat, but the total amount of protein and fat burned remained the same.

[1] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Pt. 1, p. 128.
[2] Bartmann, A.: Z. f. Biol., 1912, **58**, 375.

This experiment was duplicated by Richardson and Mason[1] when they determined the basal caloric requirement of a diabetic man and then gave a diet equal to the replacement value of the metabolism of the day. They called the diet a *replacement diet.* The diet was administered in small equal portions every two hours in order to minimize the fluctuations in both the absorption and metabolism of the food administered. The result of one of their experiments is here recorded.

THE EFFECT OF A "REPLACEMENT DIET." FOOD EATEN COMPARED WITH FOOD OXIDIZED IN 24 HOURS

Date	Diet Calories				Metabolized Calories			
	Protein	Fat	Carbohydrate	Total	Protein	Fat	Carbohydrate	Total
Jan. 20.....	0	0	0	0	243	824	57	1124
" 21.....	301	826	0	1126	299	901	6	1206
" 23.....	300	1237	0	1537	407	789	0	1196

Even when fat was given in excess there was no evidence of specific dynamic action. The authors say, "The tissues of these undernourished diabetics seem to soak up fat like a sponge."

One reason why the ingestion of fat up to the requirement does not alter the metabolism may be found in the observation of Schulz[2] that in starvation there is an increase in the quantity of fat in the blood, and of Rosenfeld[3] that the amount of fat in the liver increases. He finds that a fasting liver contains 10 per cent. of fat. If carbohydrates or protein (which yields carbohydrate in metabolism) be ingested, the fat content falls to 6.2 per cent. If fat be given to a fasting dog, the liver may contain 25 per cent. of fat; but if carbohydrates are ingested at the same time, the liver does not retain the fat, which must be deposited elsewhere. Thus, in the liver there is an antagonism between glycogen deposit, which follows carbohydrate ingestion, and fat deposition.

Pflüger[4] gave a dog fat alone in large quantities for thirty days and found that the fresh substance of the liver at the end of the period contained 45 per cent. of fat and no glycogen.

Miescher found fat globules in the muscle-cells of salmon after their five to fifteen months' fast in fresh water, during which time

[1] Richardson, H. B., and Mason, E. H.: J. Biol. Chem., 1923, **57**, 587.
[2] Schulz, F. N.: Pflüger's Arch. gesam. Physiol., 1896–97, **65**, 299.
[3] Rosenfeld, G.: Ergeb. d. Physiol., 1903, **2**, Pt. I, 86.
[4] Pflüger, E.: Pflüger's Arch. gesam. physiol., 1907, **119**, 123.

they had laid their eggs. It is undoubted that the deposits of fat in the adipose tissue of these fishes are drawn on in starvation, and that the blood then carries to the hungry cells all the fat they require for their continued function. Greene[1] states that large quantities of fat (15 per cent.) are present in the fibers of the great lateral muscle of the Columbia River salmon at the beginning of its travels up the river, and this fat remains there in strikingly uniform quantity during the whole of the migration journey. On the return journey to the sea the fat content is only 2.2 per cent. It seems that the fat supply to the cells is regulated by the quantity of other foods available, and that even in starvation there is at first ample fat to meet the requirement of the organism (see p. 108). These are important principles which will be further discussed when the subject of fatty infiltration is considered. (See page 685.)

The method of the oxidation of fat has already been described (see p. 217), and one would expect to find β-oxybutyric acid as an end-product of this metabolism. In fact, the blood of normal human subjects, as well as the blood of dogs, pigs, and cattle, contains usually a little less than 1.5 mg. of β-oxybutyric acid in 100 c.c.[2] Sassa[3] reports between 1 and 2 mg. to be widely distributed in the blood and organs of man and various mammals. In normal conditions this end-product is, therefore, present in only minimal amounts.

When fat is oxidized in excess, as in fasting, β-oxybutyric acid appears in the urine (see p. 218). So also when fat forms the main portion of the diet the same phenomenon occurs. According to Hubbard[4] ingested fat and body fat, when oxidized, yield the same amount of aceton bodies. His evidence is to be found in the following table:

	Food Calories	Distribution of Calories			Aceton	β-hydroxybutyric Acid
		Protein	Carbohydrate	Fat		
					Gm.	Gm.
Period I.....	1800	10% (45 gm.)	10% (45 gm.)	80% (160 gm.)	0.072	0.091
Period II.....	360	45 gm.	45 gm.	None	0.055	0.093

[1] Greene, C. W.: J. Biol. Chem., 1912, **11**, p. xviii; 1919, **39**, 435.
[2] Marriott, W. McK.: *Ibid.*, 1914, **18**, 507.
[3] Sassa, R.: Biochem. Z., 1914, **59**, 362.
[4] Hubbard, R. S.: J. Biol. Chem., 1923, **55**, 357.

In both cases the body was on the border line of acidosis (see p. 662).

The work of Bloor[1] has shown that after giving fat to a dog there is a gradual rise in the fat content of the blood, the maximum being attained in the sixth hour, after which there is a fall. The following shows an example:

	Blood-fat Per Cent.
24 hours after food	0.6
$3\frac{1}{4}$ hours after 100 c.c. olive oil	0.73
$6\frac{1}{4}$ hours after 100 c.c. olive oil	1.20
8 hours after 100 c.c. olive oil	0.87

Furthermore, when fat was injected intravenously in such quantity that the fat content of the blood was doubled, the excess disappeared within five minutes after the cessation of the injection.

Work of fundamental character by Magnus-Levy[2] showed the influence of the ingestion of very fat bacon upon the metabolism of the dog. Respiration experiments lasting about thirty minutes each, using the Zuntz method, were made upon a dog breathing through a tracheal cannula. These showed that after administering 140 grams of fat bacon the metabolism increased from the end of the third hour through the eighth to a height which was about 10 per cent. above the original basal level as measured twenty-four hours after the last ingestion of food. After 320 grams of fat bacon had been taken the metabolism showed a maximal increase of 19 per cent. from the end of the third hour through the sixth. The increased metabolism extended from the fourth to the thirteenth hours after food ingestion, and then subsided to the original basal level. The total increase in heat production could be estimated as 2.5 per cent. of the energy content of the fat ingested. The environmental temperature of the dog varied between 16° and 19°, and all extraneous movements were avoided.

In man, after the administration of 210 grams of butter, Magnus-Levy noted a maximal increase of 9 to 14 per cent. above the basal metabolism during the seventh hour. During the eighth hour the increase was only 6 to 8 per cent. above the basal metabolism.

The influence of external temperature on the heat production after ingesting fat above the requirement is similar to that after meat

[1] Bloor, W. R.: J. Biol. Chem., 1914, **19**, 1.
[2] Magnus-Levy, A.: Pflüger's Arch. gesam. Physiol., 1894, **55**, 1.

ingestion, only not so pronounced. Rubner[1] gives the following table, showing the effect of the ingestion of 171.3 calories in fat per kilogram of dog:

SPECIFIC DYNAMIC ACTION OF FAT

171.3 calories in fat per kg. dog were ingested

Temperature	Calories per Kilo		Increase
	Starvation	After Fat Ingestion	
2.7°	152.1	155.5	+2.2 per cent.
15.5°	83.1	93.4	+12.4 "
31.0°	64.5	79.9	+23.9 "

At 2.7° the excess ingested above the requirement amounted to 12.6 per cent., and the increase in heat production was 2.2 per cent. At 31° the excess of food calories above the requirement was 165 per cent., and the increase in heat production was 23.9 per cent. In this instance 100 per cent. of the requirement may be calculated to raise the metabolism 14.4 per cent. at a temperature of 31°. This represents the specific dynamic effect of fat on the metabolism.

Murlin and Lusk[2] were not able to find so great a specific dynamic action in the dog as Rubner found. They gave to a dog an emulsion containing 75 grams of fat with 692 calories of energy, or 145 per cent. of the basal energy requirement of the animal. The total increase of heat production was 28.8 calories or 4.1 per cent. of the energy in the fat. The experiments were carried out at an environmental temperature of 26° to 27° in a respiration calorimeter, and the results are plotted in the form of a chart, as shown on p. 314. (For the effect of glucose and fat see also p. 387.)

The experiment shows that after the ingestion of fat the heat production gradually rises till the sixth hour to a maximum 30 per cent. above the basal metabolism, and then falls slowly to the basal level, which is reached ten hours after the fat has been taken (Fig. 22). This curve of increasing metabolism accords with the curve of increasing fat content in the blood as shown by Bloor, and indicates that the heat production may be increased by increasing the number of metabolites available for cell nutrition. It may be defined as the *metabolism of fat plethora.*

It appears from the respiratory quotients that the increase in heat production is entirely at the expense of ingested fat. The respiratory quotients as determined for the basal metabolism averaged 0.84, and

[1] Rubner, M.: "Energiegesetze," 1902, p. 119.
[2] Murlin, J. R., and Lusk, G.: J. Biol. Chem., 1915, **22**, 15.

after fat ingestion 0.79. Calculation showed that the amounts of protein and glycogen oxidized during the two series of experiments were identical, so that *the extra heat production after giving fat was derived from fat itself.*

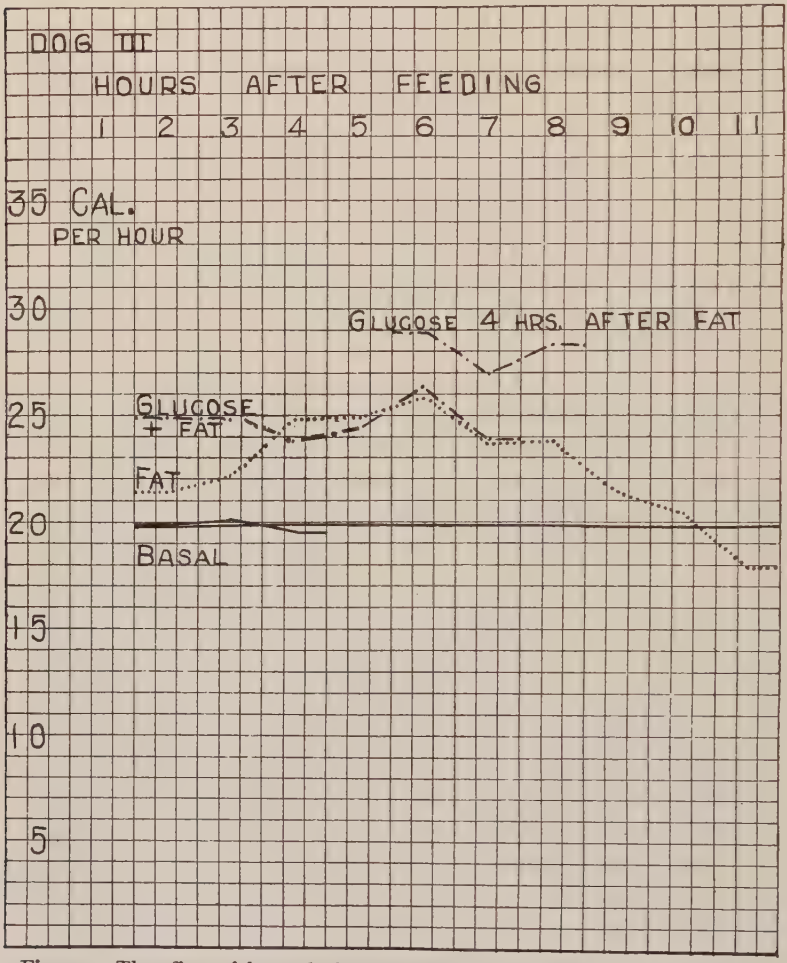


Fig. 22.—The effect of fat and of glucose plus fat upon the heat production.

It has already been demonstrated that less protein is burned in starvation when the body is fat than when it is lean. It would, therefore, seem that if protein and fat were ingested together, a similar reduction in the amount of the protein requirement would be effected (Voit).

It has been shown in a previous chapter that nitrogenous equilibrium can be maintained in a dog only after the ingestion of three and a half times the quantity of protein destroyed in starvation (see p. 188).

E. Voit and Korkunoff,[1] continuing these experiments, find that if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1.6 and 2.1 times the starvation minimum. Much less protein food is, therefore, required to maintain the body's protein when it is ingested with fat than when it is given alone.

Thus Thomas[2] could not maintain nitrogen equilibrium when twice the amount of the fasting nitrogen elimination was given to a man in the form of meat alone, but was able to accomplish this when meat to the extent of that destroyed in fasting was administered with fat. In consequence of this, protein is more readily added to the body when fat is ingested with it, as is seen in the following experiment of Rubner[3] on a man:

INFLUENCE OF FAT INGESTION ON NITROGEN RETENTION

Food in Gm.			N Metabolism in Gm.	
N	Fat	Carbohydrates	N in Excreta	N to Body
23.6	99	260	26.36	−3.64
23.5	195	226	21.55	+1.85
23.0	214	221	18.5	+4.13
23.4	350	234	17.6	+5.75

With increasing quantities of fat there is an increasing addition of protein to the body.

It has already been shown that protein ingested alone in large quantity establishes nitrogen equilibrium at a higher level, constantly raising the amount of heat produced until nitrogenous equilibrium is reached (the secondary dynamic rise, p. 278).

The same destruction of the easily oxidized protein takes place when it is given with fat, as was shown by Voit[4] in the following experiment on a dog:

[1] Voit, E., and Korkunoff, A.: Z. f. Biol., 1895, **32**, 117.
[2] Thomas, K.: Arch. f. Physiol., 1910, Suppl., p. 249.
[3] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 2d ed., 1903, **1**, p. 43.
[4] von Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Pt. 1, p. 131.

THE "SECONDARY RISE" IN PROTEIN METABOLISM ON A MEAT-FAT DIET

(Weights in grams)

Food			
Meat	Fat	Urea	Flesh to Body
1800	0	127.9	26
1800	0	127.6	26
1800	250	117.9	162
1800	250	113.5	171
1800	250	120.7	
1800	250	115.7	164
1800	250	119.7	
1800	250	127.5	11
1800	250	130.0	

A prolonged deposition of protein in the normal adult, when fat is given with it, is demonstrably difficult.

The question arises, Does the ingestion of large quantities of fat also cause an increase in the metabolism until fat combustion is balanced by its ingestion?

Rubner[1] has shown that this is not the case. He cites the record of the following long respiration experiment on a dog which was given 80 grams of meat and 30 grams of fat daily:

ABSENCE OF THE "SECONDARY DYNAMIC RISE" IN FAT METABOLISM ON A MEAT-DIET

(Fat being given in excess of the requirement)

Calories of Metabolism		
Protein	Fat	Total
97.2	173.0	270.0
83.0	178.0	261.1
89.3	173.5	262.7
85.6	163.2	248.9
87.8	169.0	256.8
83.0	159.6	242.6
74.4	171.7	246.2
78.0	178.4	256.3
80.0	179.6	259.7

The diet was 58.7 per cent. above the starvation requirement. It contained 354 calories, of which 21.5 per cent. were in protein. The mean heat production during the period of ingestion of food was 256.0 calories, and in the following starvation days 223.2 calories, showing an increase in metabolism of 11.2 per cent. caused by an excess in food of 58.7 per cent. During the later days the animal was in nitrogenous equilibrium. Notwithstanding an excess of fat in the diet, and a continued deposit of fat in the body, there was no increase in the metabolism during the time of experimentation. The secondary dynamic action noted by Rubner as regards protein does not, therefore, take place as regards fat. The storage of fat in the body is consequently a matter of comparative ease.

[1] Rubner, M.: "Energiegesetze," 1902, p. 251.

Rubner[1] has compared the metabolism of a boy who was obese with that of his brother, who was a year older, but thin. They were the children of parents of small means and would not naturally be overfed. The interesting point of the experiment was whether obesity was due to a reduced metabolism with the consequent deposition of fat. To each boy was given a maintenance diet, or one which balanced his metabolism, without adding to or subtracting from his body substance. The general results are as follows:

	Fat Boy	Thin Boy
Age in years	10	11
Weight in kilograms	41	26
Total calories of metabolism	1786.1	1352.1
Calories per kilogram	43.6	52.0
Calories per sq. m. surface	1321	1290

The comparison shows that the fat brother had a larger total metabolism than the thin one, but the fat boy also had the larger surface. Per square meter of surface the metabolism was the same (see p. 139). The gradual increase in the area of the body caused by filling out the fat cells may therefore increase combustion, but this is not due to the specific action of the fat on metabolism as in the case of the secondary dynamic rise after protein ingestion, but rather to the increase in the size of the body. Carbohydrates, which in excess are converted into fat, must behave in the same way.

Strouse, Wang, and Dye[2] could find no essential difference in the basal metabolism of three women of the same height and of different weights, and conclude that a lowered basal metabolism is not the cause of obesity. The following table records these observations:

STUDIES ON THE METABOLISM OF OBESITY. BASAL METABOLISM

Types (All Women)	Height	Weight	Heat Production					
			Cals. in 24 Hrs.			Cals. per Sq. M. per Hr.		
			Observed	Harris-Benedict Standard	Dif.	Observed	Du Bois Standard	Dif.
	Cm.	Kg.			Per cent.			Per cent.
Normal subject	160	55.5	1455	1369	+6.3	38.6	37.0	+4.3
Underweight	159.4	41.6	1265	1249	+1.3	38.2	37.0	+3.3
Overweight	159.5	140.0	2119	2135	−0.7	38.4	36.5	+5.2

[1] Rubner, M.: "Beiträge zur Ernährung im Knabenalter," Berlin, 1902.
[2] Strouse, S., Wang, C. C., and Dye, M.: Arch. Int. Med., 1924, **34**, 275.

Mason[1] records that the administration of a fatty meal consisting of 200 c.c. of 20 per cent. cream, 40 gm. of butter, and 30 gm. of toast caused an extraordinary rise in the heat production of an undernourished woman, which reached its maximum level at the end of the 2d hour. The reaction was much greater than normal, and greater than when the person later became well nourished. Fat was more potent than meat (see p. 306). The compensating level of reduced metabolism in undernutrition was immediately destroyed in the presence of ample fuel in the form of fat.

This result is different from that observed by Richardson and Mason (see p. 310), who gave an excess of fat in small quantities every 2 hours to an emaciated diabetic and noted no rise in the metabolism. The later results of Mason are apparently due to a greater amount of fat entering the system for use by the cells. In the undernourished, therefore, two forces appear: one of retention of fat by the depleted reservoirs, and another the combustion of fat in an endeavor to lift the metabolism to the level which would obtain were the individual in normal condition.

It will be noticed in the experiment on p. 316 where 80 grams of meat and 30 grams of fat were daily ingested, that although the protein metabolism gradually fell, the fat metabolism gradually rose, and in isodynamic relation to the fall in protein. Allowing for the difference in specific dynamic action, protein and fat replace each other in metabolism in isodynamic quantities.

[1] Mason, E. H.: J. Clin. Invest., 1927, **4**, 353.

CHAPTER XIV

THE INFLUENCE OF THE INGESTION OF CARBOHYDRATE

PART I—THE INTERMEDIARY METABOLISM

Modern physics inside the almost invisible structure of the atom, chemistry inside the visible structure of the molecule, anatomy inside the visible structure of the tissue and biochemistry inside the visible structure of the cell.—A. V. Hill.

The preceding chapters have dealt entirely with the subject of the metabolism of protein and fat. The metabolism of carbohydrate has been touched upon incidentally in describing the intermediary metabolism of protein, but the fuller details remain to be considered. Generally speaking, two-thirds of the energy produced by the human organism is derived from the oxidation of carbohydrate. Not without warrant is bread considered the staff of life.

Normal urine contains small amounts of carbohydrate. Neuwirth[1] states that the total quantity excreted by 26 individuals varies between 1.38 and 0.61 gm. per day, of which 0.49 to 0.13 gm. are fermentable and between 1.02 and 0.37 gm. consist of non-fermentable reducing substances. The amount of sugar excreted falls with a restriction of the food intake. Van Slyke has recently denied the existence of fermentable sugar in normal urine (unpublished).

GLYCOGEN

The gastro-intestinal tract converts starches into glucose, transforms sucrose into glucose and fructose, and lactose into glucose and galactose, so that these soluble monosaccharids become the fuels transported by the blood for the nourishment of the body-cells. The enzymes maltase, sucrase, and lactase which, respectively, convert maltose, sucrose, and lactose into monosaccharids, are present in the intestinal mucosa of the newborn infant.[2]

If 10 gm. of sucrose or 10 gm. of lactose are administered subcutaneously in man F. Voit[3] finds that they are completely eliminated in the urine, whereas Brahm[4] reports that when 300 gm. of sucrose or 600 gm. of invert-sugar are given orally none is eliminated in the urine.

[1] Neuwirth, I.: J. Biol. Chem., 1922, **51**, 11.
[2] Ibrahim, J.: Z. physiol. Chem., 1910, **66**, 19.
[3] Voit, F.: Deut. Arch. klin. Med., 1897, **58**, 523.
[4] Brahm, C.: Biochem. Z., 1917, **80**, 242.

The writer personally prepared fructose from inulin in 1889, which when given to a fasting rabbit caused the formation in its liver of large quantities of glycogen, the anhydrid of glucose.[1] To a lesser extent the same fate may befall ingested galactose. After giving glucose or fructose, as much as 40 per cent. of the dry solids of the liver consisted of glycogen. These monosaccharids were not changed in the intestine. Carl Voit called attention to the fact that carbohydrates which were fermentable with yeast were also convertible into glycogen.

Isaac[2] perfused a fluid made up of dog's washed blood-cells and Ringer's solution containing fructose through the liver of a fasting dog and found that the fructose was converted into glucose. The change in the composition of the perfusing fluid was as seen below:

	Before Perfusion	Three Hours Later
d-Glucose	0.012 per cent.	0.310 per cent.
d-Fructose	0.349 "	0.020 "

This transformation is dependent on the vitality of the liver cells, for liver extracts will not accomplish it, nor will living muscle.[3]

Ishimori[4] has reported that glycogen deposition in the liver follows the intravenous injection of glucose and fructose in the rabbit, although galactose does not have this effect. Galactose is less readily oxidized, at least in the adult organism, than are the other two hexoses (see p. 381), though it may be that the conditions for its breakdown are more favorable in the suckling.

The quantity of glycogen present in a living animal cannot be accurately estimated. Schöndorff[5] gave seven dogs diets rich in carbohydrate for several days, and found that the quantity of glycogen present in their bodies varied between 7.59 and 37.87 grams per kilogram.

The percentage distribution of this glycogen in 100 grams of the fresh tissue varied as follows:

	Maximum	Minimum
Liver	18.69	7.3
Muscle	3.72	0.72
Heart	1.32	0.104
Bone	1.90	0.197
Intestines	1.84	0.026
Skin	1.68	0.09
Brain	0.29	0.047
Blood	0.0066	0.0016

[1] Voit, C.: Z. f. Biol., 1891, **28**, 245.
[2] Isaac, S.: Z. physiol. Chem., 1914, **89**, 78.
[3] Isaac, S., and Adler, E.: *Ibid.*, 1921, **115**, 105.
[4] Ishimori, K.: Biochem. Z., 1912–13, **48**, 332.
[5] Schöndorff, B.: Pflüger's Arch. gesam. Physiol., 1903, **99**, 191.

The traditional distribution of glycogen, one-half to the liver and one-half to the rest of the body, Schöndorff shows to be incorrect. For 100 grams of liver glycogen there occurred in the rest of the body the following amounts:

Dog	I	398 grams.
"	II	279 "
"	III	87 "
"	IV	76 "
"	V	159 "
"	VI	355 "
"	VII	105 "

Junkersdorf[1] has given to 4 normal dogs weighing 10 kg. each a normal diet, the constituents of which were in the same relative proportions as Voit's standard diet for man. He then killed them and analyzed their organs for glycogen. The average of these analyses may be grouped as follows:

	Weight	Per Cent. of Body Weight	Glycogen Content		
			Of Organ	Average in Organ	Maximum in Organ
	Gm.		Per Cent.	Gm.	Gm.
Muscle	3130	31.3	0.55	17.22	24.41
Heart	79	0.79	0.47	0.37	0.37
Liver	270	2.7	6.1	16.47	18.79
Kidney	47	0.47	0.15	0.07	0.07
				34.13	43.62

The maximum glycogen content of muscle was 0.78 per cent.; of liver 7 per cent. Evidently the well-nourished dog contains between 0.3 and 0.4 per cent. of its body weight in the form of glycogen.

Moulton[2] reports that in the muscle, computed on the fat-free basis, of a very fat steer there is 0.46 per cent. of glycogen, and in the muscle of a very thin steer of the same age 0.51 per cent.

An old observation of Külz[3] shows that an active organ like the dog's heart maintains its normal glycogen content even after the dog has undergone prolonged and severe exercise accompanied by fasting. Junkersdorf[4] finds that on the 11th day of fasting the average glycogen content of the liver in the dog is 0.59 per cent. and of the muscle 0.21 per cent. Applying these values to a dog weighing 10 kg., one

[1] Junkersdorf, P.: Pflüger's Arch. gesam. Physiol., 1925, **210**, 351.
[2] Moulton, C. R.: J. Biol. Chem., 1920, **43**, 67.
[3] Külz, E.: "Festschrift zu Ludwig," Marburg, 1891, p. 109.
[4] Junkersdorf, P.: Pflüger's Arch. gesam. Physiol., 1921, **186**, 238.

may estimate that the muscles may still contain 6.57 gm., the liver 1.59 gm., and the whole animal 8 gm. or 0.08 per cent. of glycogen on the 11th day of fasting.

Hoffmann and Wertheimer[1] state that after large carbohydrate ingestion the denervated muscle of the dog may contain 0.46 per cent. of glycogen, whereas if the muscle be stimulated electrically daily it may contain 0.74 per cent. of glycogen. As in the beating heart, muscular activity favors glycogen retention.

In *phlorhizin diabetes* in the dog on the 10th day of administering the drug, during the course of which small amounts of meat were given, Reilly, Nolan, and Lusk found on killing the animal 0.08 per cent. of glycogen in the liver; in another phlorhizinized dog 0.13 per cent. was in the liver, 0.37 per cent. in the muscle. On the 3d day of fasting and phlorhizin administration Junkersdorf[2] found that the dog's liver (average of 10 dogs) contained 0.06 per cent. of glycogen and the muscle 0.20 per cent. Finally, Junkersdorf[3] reports that a dog that had fasted 5 days and had been given phlorhizin twice daily (urinary D:N = 3.12) had in the heart 0.8 per cent., in the liver 0.02 per cent., and in the muscle 0.03 per cent. of glycogen. Under these most acute circumstances of carbohydrate depletion the active heart preserved the content of glycogen necessary for its proper functioning. The low glycogen content of the muscle corresponds to a period of great muscular weakness, hypoglycemia, aceton breath, coma, followed by convulsions and often death (see pp. 444, 634). The convulsions may be prevented by giving glucose, or protein which is convertible into glucose, but never by giving fat, which is not convertible into glucose in the animal body as will be shown in the chapters on Diabetes.

The Influence of Insulin on Glycogen Formation.—It is necessary to speak of insulin at this point even before its more extended treatment in the chapter on diabetes, for the whole subject of carbohydrate metabolism is here involved. Briefly, the depancreatized dog cannot oxidize glucose nor hold glycogen in its liver. Administration of insulin, a product of the islands of Langerhans located in the pancreas, restores both functions.[4]

[1] Hoffmann, A., and Wertheimer, E.: Pflüger's Arch. gesam. Physiol., 1927, **216**, 337.
[2] Junkersdorf, P.: *Ibid.*, 1922, **197**, 500.
[3] Junkersdorf, P.: *Ibid.*, 1923, **200**, 443.
[4] Banting, F. G., Best, C. H., Collip, J. B., Hepburn, J., and Macleod, J. J. R.: Trans. Roy. Soc. Canada, 1922, p. 16.

A very complete modern analysis of the comparative influence of fasting, meat ingestion, glucose and fructose ingestion upon the glycogen content of the heart, liver, and muscles of normal and completely depancreatized dogs is found in the subjoined table taken from the work of Fischer and Lackey.[1]

THE AVERAGE GLYCOGEN CONTENT OF THE HEART, LIVER AND MUSCLES OF NORMAL AND DIABETIC DOGS

No. of Dogs	Condition	Food	Days	Heart	Liver	Muscle
		Per Kg. Body Weight		Per Cent.	Per Cent.	Per Cent.
2	Normal	Fast	5	0.28	0.26	0.09
2	Depancreatized	Fast	4	0.48	0.07	0.16
3	Depancreatized	Fast	5	0.18	0.045	0.046
3	Normal	28.6 gm. meat	5	0.50	1.81	0.58
4	Depancreatized	28.6 gm. meat	5–6	0.8	0.11	0.31
1	Normal	28.6 gm. meat + 4.4 gm. glucose	5	0.5	1.52	0.71
1	Normal	28.6 gm. meat + 4.4 gm. fructose	2	0.46	4.63	0.57
1	Diabetic	28.6 gm. meat + 4.4 gm. glucose	13	1.09	0.045	0.26
1	Diabetic	28.6 gm. meat + 4.4 gm. fructose	2	0.52	0.048	0.16
1	Diabetic	28.6 gm. meat + 4.4 gm. fructose	4	0.93	0.05	0.28

In 12 normal dogs the average glycogen content of heart muscle is 0.44 per cent., and in 13 depancreatized dogs 0.79 per cent. The authors confirm the work of Cruickshank[2] that completely depancreatized dogs do not store glycogen from fructose.

It is evident that the depancreatized dog, like the normal dog, maintains an ample supply of glycogen in its heart, that when favored with a diet containing meat or meat with glucose or fructose, the glycogen content of the muscle is fairly well maintained, but that in every instance the liver loses its capacity to retain more than traces of glycogen. Administration of insulin to the diabetic animal, however, enables the liver to store glycogen so that nearly normal values are obtained. On the other hand, administration of large doses of insulin to normal dogs causes the liver to discharge glycogen, evidently to furnish fuel.

Dr. and Mrs. Cori[3] found that if glucose is given *per os* the blood sugar in the femoral artery is greater than in the femoral vein, a phenomenon accentuated by insulin. They concluded that the

[1] Fischer, N. F., and Lackey, W. R.: Am. J. Physiol., 1925, **72**, 43.
[2] Cruickshank, E. W. H.: J. Physiol., 1913–14, **47**, 1.
[3] Cori, C. F., and Cori, G. T.: J. Biol. Chem., 1926, **70**, 557.

muscles removed glucose from the blood. When insulin is given to diabetics these reflect the same phenomenon.

Best, Dale, Hoet, and Marks[1] state that the glucose intravenously injected which disappears from an eviscerated spinal cat preparation under the influence of insulin is equal to the sum of the glycogen deposited in the muscles and the glucose-equivalent of the oxygen absorbed. They also say, "Attributing to insulin when present in excess no other action than the production of its known physiological effects with more than physiological intensity, and without any assumption of unknown and unrecognizable forms of carbohydrate, we believe that it will prove possible to account for all its effects, in any dosage, on any species."

This statement is beautifully illustrated by the work of Cori and Cori.[2] They allowed rats to fast 48 hours, at which time the liver glycogen averaged 0.114 per cent. and the respiratory quotient was 0.71. They then administered glucose to one group of animals and glucose plus insulin to another. Their results appear in the table.

THE RELATION BETWEEN SUGAR OXIDATION AND GLYCOGEN FORMATION IN NORMAL AND IN INSULINIZED RATS

(Values per 100 gm. body weight per 4 hours)

	Glucose (14 Rats)		Glucose + Insulin (10 Rats)	
Glucose absorbed, gm.	0.75		0.77	
Glucose oxidized, gm.	0.28		0.38	
Glycogen formed, gm.	0.39		0.32	
Glucose recovered, gm.	0.67		0.70	
Sugar accounted for, per cent.	89		92	
Blood sugar, gm.	0.18		0.08	
Respiratory quotient	0.84		0.88	
Urine N, mg.	12.2		12.3	
Calories: from protein	0.30		0.31	
from fat	1.11		0.68	
from CH	1.05	2.46	1.41	2.40

It is therefore evident that insulin in excess causes increased carbohydrate oxidation and that in both normal and insulinized rats the sum of the glucose oxidized and the glucose converted into glycogen was within 90 per cent. of the glucose absorbed by the animals.

Finally, it is of interest to learn from the experiments of Best, Hoet, and Marks[3] that the decrease or complete disappearance of the

[1] Best, C. H., Dale, H. H., Hoet, J. P., and Marks, H. P.: Proc Roy. Soc. (London), 1926, B, **100**, 55.

[2] Cori, C. F., and Cori, G. T.: J. Biol. Chem., 1926, **70**, 557.

[3] Best, C. H., Hoet, J. P., and Marks, H. P.: Proc. Roy. Soc. (London), 1926, B, **100**, 32.

muscle glycogen in normal rabbits produced by large doses of insulin is chiefly due to convulsions. For if the muscles on one side be denervated so they cannot contract and convulsions be induced the following relations are discovered:

	Normal Per Cent.	Denervated Per Cent.
Tibialis	0.01	0.73
Gastrocnemius	0.03	0.39

Although the muscle glycogen disappears during the hypoglycemic convulsions after giving insulin, Dudley and Marrian[1] find no reduction in the glycogen content of the heart muscle, as is witnessed below:

	Normal Rabbit Glycogen Per Cent.	Insulin Rabbit (after Convulsion) Glycogen Per Cent.
Liver	5.53	1.86
Heart	0.26	0.54
Skeletal muscles	0.57	0

It is highly probable that a diabetic dog, the liver of which contains no glycogen, can be rendered free from glycogen by convulsions except for that retained in the heart. It would be interesting to know whether under these circumstances the respiratory muscles, like the heart, are more retentive of glycogen than are the larger skeletal muscles. The origin of glycogen in fasting after convulsions has already been discussed (see p. 107).

In the various discussions on the subject of glycogen it has been shown that in starvation, and after protein and sugar ingestion, there is glycogen present in the body—a constant supply always ready for emergencies, which can be reduced through exercise, but which is only to be completely removed by tetanic convulsions (pp. 107 and 444).

The writer has here avoided the discussion of a production of sugar from fat. To his mind the evidence is against such production, as will be demonstrated in the chapter on Diabetes.

THE INTERMEDIARY METABOLISM OF ALCOHOLIC FERMENTATION

Glucose, synthesized by the green leaf of the plant under the influence of sunlight, is the food not only of man and animals but also of yeast and of microörganisms in general.[2] It may be of interest to consider the chemistry of the behavior of yeast.

[1] Dudley, H. W., and Marrian, G. F.: Biochem. J., 1923, **17**, 435.

[2] Consult A. Harden: "Alcoholic Fermentation," London, 3d ed., 1923, with its admirable historical introduction; F. F. Nord, "Chemical Processes in Fermentations," Chem. Rev., 1926, **3**, 41; and C. Oppenheimer: "Die Fermente und ihre Wirkungen," Leipzig, 5th ed., 1925 and 1926, in 2 vols. and 2037 pages.

Gay-Lussac[1] in 1815 discovered the quantitative relations of alcoholic fermentation expressed in the modern chemical formula:

$$C_6H_{12}O_6 = 2CO_2 + 2C_2H_5OH.$$

This is "la vie sans air" of Pasteur.

Young[2] showed that the great acceleration of fermentation which takes place when phosphate is added to a fermenting solution of d-glucose, d-fructose, or d-mannose is due to the formation of a hexose diphosphate which yields fructose.

$$\begin{array}{l} CH_2(PO_4H_2) \\ | \\ CO \\ | \\ C_4H_5O_3(PO_4H_2) \end{array}$$

This was confirmed by Harden and Young[3] and by Neuberg.[4]

Lebedew[5] was the first to obtain a definite phenylhydrazin salt of hexosemonophosphoric acid from the hexose diphosphate of Young, and this was afterward confirmed by Young[6] himself. The older knowledge that mineral salts were necessary for alcoholic fermentation was therefore amplified into a knowledge that a hexosephosphate was necessary for the reaction.

Willstätter and Sobotka[7] can find no difference in the rapidity of fermentation between glucose and fructose or between α- and β-glucose. If all pass by enolization (see p. 330) into fructose and fructose diphosphate, then the chemistry of fermentation would be the same for all.

It was discovered by Harden and Young[8] in 1905 that filtered yeast juice obtained by ultra-filtration, which contains the essential ferment of yeast, the zymase of Buchner, and is a solution which soon loses its potency to ferment glucose, may be rendered doubly active if mixed with an equal volume of *boiled* filtrate in which the zymase has been destroyed and which of itself will not ferment glucose. The boiled filtrate contains the co-enzyme. The co-enzyme must act with zymase if the latter is to be effective. Whether the

[1] Gay-Lussac, L. J.: Ann. de Chim. et de Phys., 1815, **95,** 311.
[2] Young, W. J.: Proc. Roy. Soc. (London), 1909, B, **81,** 528.
[3] Harden, A., and Young, W. J.: Biochem. Z., 1911, **32,** 173.
[4] Neuberg, C., Färber, E., Levite, A., and Schweink, E.: *Ibid.*, 1917, **83,** 244.
[5] Lebedew, A.: *Ibid.*, 1909, **20,** 114; *Ibid.*, 1910, **28,** 213.
[6] Young, W. J.: *Ibid.*, 1911, **32,** 177.
[7] Willstätter, R., and Sobotka, H.: Z. physiol. Chem., 1922, **123,** 164, 170.
[8] Harden, A., and Young, W. J.: Proc. Roy. Soc. (London), 1906, B, **77,** 405.

co-enzyme is specifically associated with the formation of hexose phosphate or not is unknown. Neuberg conceives that the co-enzyme is nothing more than stimulating aldehyd radicles which are present in the filtered yeast juice and are not destroyed by boiling.

Neuberg[1] calls attention to the fact that the modern formula of glucose carries in it nothing which looks like either alcohol or carbon-dioxid. The formula of Gay-Lussac tells nothing of the intermediary steps. Contemplation of it was not productive of progress; only new facts could bring information. The first fact initiating a new era was the discovery by Neuberg and Wastenson[2] in 1910 of the rapid conversion of pyruvic acid into acetaldehyd and CO_2 by an effective enzyme *carboxylase* which always accompanies yeast zymase. One can destroy *zymase* so that there is no fermentation of glucose and yet produce fermentation of pyruvic acid through the presence of carboxylase. Zymase acts on glucose, fructose, and galactose; carboxylase on pyruvic acid and the α-keto acids produced in the oxidative deamination of amino-acids, causing the keto acids to lose CO_2. As the aldehyds which result in the oxidative deamination and de-carboxylation of amino-acids are highly stimulating, Neuberg suggests that they may be the co-enzyme of Young. For Neuberg and Ehrlich[3] show that there are 71 aldehydes of many kinds, all of which promote the fermentation of glucose by yeast, affording the strongest kind of stimulation. Glycolaldehyd exerts a strong catalytic power.[4]

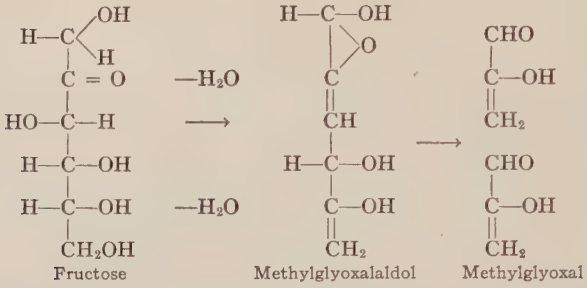
Neuberg and von May[5] have fermented 35.4 gm. of pyruvic acid and, by adding a precipitant for acetaldehyd, have recovered 10.7 gm. of that substance, thus demonstrating its large production in the intermediate metabolism of pyruvic acid. They also recovered 4.65 gm. of acryloin, a synthetic compound formed from the condensation of two molecules of pyruvic acid:

$$2CH_3—CO—COOH = 2CO_2 + \underset{\text{Acryloin}}{CH_3—CO—CHOH—CH_3}.$$

The balance sheet shows that 16.03 gm. of CO_2 were given off, making a total of 31.4 gm. accounted for against 35.4 gm. of pyruvic acid originally employed.

[1] Neuberg, C.: Festschrift der Kaiser Wilhelm Ges., 1921, p. 162.
[2] Neuberg, C., and Wastenson, H.: Zentralbl. f. Physiol., 1911, **25**, 99.
[3] Neuberg, C., and Ehrlich, M.: Biochem. Z., 1920, **101**, 239.
[4] Neuberg, C., and Sandberg, M.: *Ibid.*, 1920, **109**, 290.
[5] Neuberg, C., and v. May, A.: *Ibid.*, 1923, **140**, 299.

Neuberg's conception of the preliminary steps in the fermentation of fructose involves the following transformations:



At this stage two molecules of methylglyoxal may interact with water with the formation of glycerol and pyruvic acid (first Cannizzaro reaction).

$$CH_2{:}COH{-}CHO + H_2 = CH_2OH{-}CHOH{-}CH_2OH$$
$$CH_2{:}COH{-}CHO + O = CH_2{:}COH{-}COOH$$

Pyruvic acid, which is being constantly produced, is constantly passing into acetaldehyd and carbondioxid as follows:

$$CH_3{-}CO{-}COOH = CO_2 + CH_3CHO$$

Then methylglyoxal and acetaldehyd undergo the second Cannizzaro reaction and pyruvic acid and alcohol result.

$$\begin{matrix} CH_2{:}COH{-}CHO + O \\ CH_3{-}CHO + H_2 \end{matrix} \longrightarrow \begin{matrix} CH_3{-}CO{-}COOH \\ CH_3CH_2OH \end{matrix}$$

Neuberg and Oppenheimer[1] state that these reactions are brought about by the following enzymes:

1. Enzymes of primary attack: hexoses (zymase).
2. Phosphatases, synthetic (hexose phosphate forming); analytic (hexose phosphate splitting).
3. Aldehydase (forming methyl-glyoxal).
4. Keto-aldehyd mutase (Cannizzaro reaction).
5. Carboxylase (CO_2 elimination).
6. Carboligase (or acryloinase), a ferment bringing about the synthesis of acryloin.

[1] Neuberg, C., and Oppenheimer, C.: Biochem. Z., 1925, **166**, 450.

In the anaerobic *lactic acid fermentation*[1] the ketoaldehyd mutase is inactive and methylglyoxal passes directly and completely into lactic acid by the glycolytic ferment.

$$CH_3—CO—CHO + H_2O = CH_3—CHOH—COOH$$

In *acetic acid fermentation*[2] two molecules of acetaldehyd react together as follows:

$$\begin{matrix} CH_3CHO + H_2 \\ \| \\ CH_3CHO + O \end{matrix} \longrightarrow \begin{matrix} CH_3CH_2OH \rightarrow CH_3CHO \\ \\ CH_3COOH \end{matrix}$$

The process takes a zigzag course.

Neuberg[3] thinks that *butyric acid* fermentation is fundamentally the same as yeast fermentation. Two molecules of pyruvic acid condense to form pyruvic aldol, and this passing through a lacton form results in the formation of butyric acid.

$$\begin{matrix} CH_3.CO.COOH \\ CH_3.CO.COOH \end{matrix} \longrightarrow \begin{matrix} CH_3.COH—COOH \\ | \\ CH_2—CO—COOH \end{matrix} \xrightarrow{-CO_2} \begin{matrix} H \\ | \\ OH \end{matrix} \longrightarrow \begin{matrix} CH_3.CHO \\ | \\ CH_2CO \end{matrix} \!\!> CO$$

Lacton form

$$-CO_2 \longrightarrow \begin{matrix} CH_3—CH_2 \\ | \\ CH:CO \end{matrix} + H_2O \longrightarrow CH_3.CH_2.CH_2.COOH$$

What significance or value these details may have in the story of the intermediary metabolism within the animal body is not known, but they are sometimes applied to the explanation of some of the problems encountered.

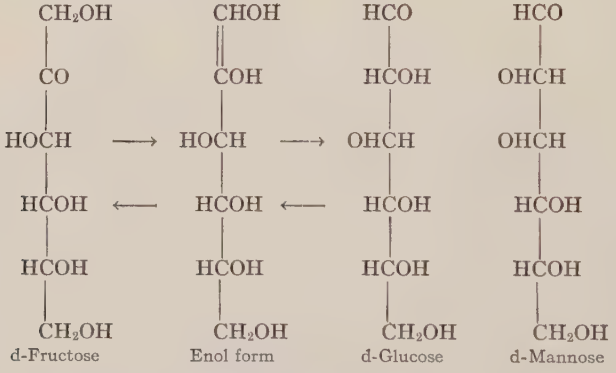
THE INTERMEDIARY METABOLISM OF CARBOHYDRATE IN THE ANIMAL BODY

The chemical transformations of sugar molecules present a fascinating field for the explorer. The literature on the subject of the metabolism of carbohydrates published during the last ten years exceeds that of all the other phases of the subject of metabolism combined. It is obviously futile to attempt a detailed consideration of the hundreds of scientific papers here involved. It is only possible to indicate here some of the scientific facts which are leading to a correct understanding of the subject. There is some unavoidable repetition of the facts presented in the chapter on The Intermediary Metabolism of Protein.

[1] Neuberg, C., and Gorr, G.: Biochem. Z., 1925, **166**, 482.
[2] Neuberg, C., and Windisch, F.: *Ibid.*, p. 454.
[3] Neuberg, C., and Arinstein, B.: *Ibid.*, 1921, **117**, 269.

Lobry de Bruyn and van Ekenstein[1] found that when glucose solutions contained mere traces of hydroxyl ions, d-mannose, d-fructose, and d-pseudo-fructose appeared, and this phenomenon, called *mutarotation*, continued until the solution no longer rotated polarized light. Other hexoses have since been discovered in the mixture. According to Nef[2] any ordinary hexose can yield 116 different substances. Of these, he was able to identify 93, of which 47 were sugars and the rest fragments of sugar cleavage. Henderson[3] finds a slow but unmistakable loss of optical activity in a glucose solution maintained at the body temperature and at the alkalinity of the blood, though the quantity of sugar present is not affected. The potency of disodic phosphate as aiding this reaction has also been reported by Murschhauser.[4]

Nef[5] suggests that the reaction d-fructose ⟶ glucose must take place through the intermediary formation of an enol. This may be written as follows:



The 1-2 enol form given above is believed to be the common intermediate which maintains an equilibrium between glucose, fructose and mannose.

Glucose behaves like a very weak acid. In the presence of alkali, mutarotation with the production of various isomeric forms is possible. The presence of traces of acid prevents these transformations as well as any oxidative changes. To the invulnerability of the glucose molecule under these circumstances has been ascribed its non-

[1] Lobry de Bruyn, C. A., and van Ekenstein, W. A.: Recueil des travaux chimiques des Pays-Bas, 1895, **14**, 158, 203; 1900, **19**, 1.
[2] Nef, J. U.: Annalen der Chemie und Pharmacie, 1907, **357**, 214.
[3] Henderson, L. J.: J. Biol. Chem., 1911–12, **10**, 3.
[4] Murschhauser, H.: Biochem. Z., 1920, **110**, 181.
[5] Nef, J. U.: Annalen d. Chemie und Pharmacie, 1907, **357**, 294.

destruction in diabetes (see p. 617). An increase in the hydrogen ion concentration of a perfusing fluid greatly reduces the utilization of glucose by an excised beating heart.[1]

The analogy between the phenomenon of Lobrey de Bruyn and the reactions which take place in the body is incomplete in that the latter always occur in one direction. Glucose, for example, is not converted into fructose within the organism.

Nef believes that the many chemical reactions of sugar may be best explained on the assumption that the sugar is in part dissociated, giving residues which may be synthesized into glucose again. Such substances might be glyceric aldehyd or methylglyoxal (see p. 233). Fragments of this sort might be open to ready oxidation in the body, or be for use as the food of yeast cells in alcoholic fermentation. When glucose or its hypothetic cleavage products, glyceric aldehyd or methylglyoxal, are treated with alkali in the presence of oxygen they are oxidized to carbon dioxid and water. *If no oxygen is present, lactic acid appears in the solution. But if lactic acid be added to an oxygenated alkaline solution of glucose, lactic acid is not destroyed. Hence, in the oxidative destruction of glucose, lactic acid is not an intermediary product.*[2]

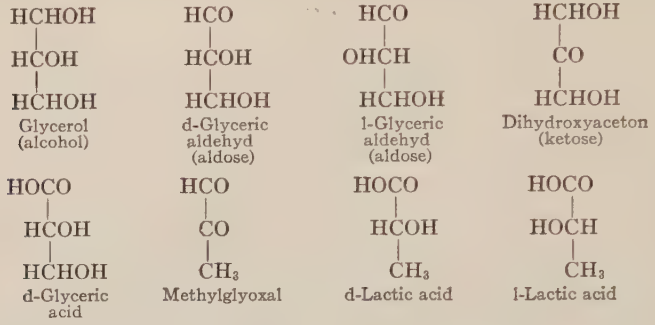
This last fact was first observed by Framm.[3] Confirmatory of this is the work of Shaffer[4] which shows that, although glucose in alkaline solution is completely oxidized by H_2O_2, lactic acid remains unoxidized.

A solution of pure glucose in water is not oxidized by H_2O_2, but when disodic phosphate is added to the solution Witzemann[5] has not been able to oxidize it completely. Furthermore, Warburg and Yabusoe[6] made the important discovery that fructose in a phosphate solution is completely oxidized by the molecular oxygen of the atmosphere even in weakly acid and neutral solutions, and that this is the only sugar so reactive. This may explain the quick combustion of fructose after its ingestion.

The relations between the *trioses* or sugars containing three carbon atoms and substances into which they are convertible are shown

[1] Rona, P., and Wilenko, G. G.: Biochem. Z., 1913–14, **59**, 173.
[2] This description is taken from Woodyatt, R. T.: Wells's "Chemical Pathology," Philadelphia and London, 4th ed., 1920, p. 642.
[3] Framm, F.: Pflüger's Arch. gesam. Physiol., 1896, **64**, 575.
[4] Shaffer, P. A.: Physiol. Rev., 1923, **3**, 404.
[5] Witzemann, E. J.: J. Biol. Chem., 1920–21, **45**, 1.
[6] Warburg, O., and Yabusoe, M.: Biochem. Z., 1924, **146**, 380.

below. All of these substances when given to a phlorhizinized dog are completely converted into glucose:



Mandel and Lusk[1] gave lactic acid to a phlorhizinized dog and found it was eliminated as extra glucose in the urine (see p. 686). They furthermore found that the d-lactic acid which is eliminated in the urine of dogs poisoned with phosphorus disappears from such urine after the administration of phlorhizin. They, therefore, concluded that lactic acid arose from the metabolism of glucose, and that when glucose, its antecedent substance, was removed by phlorhizin, lactic acid vanished from the urine. They proposed the following formula of carbohydrate metabolism:

$$\text{lactic acid} \rightleftarrows \text{glucose} \rightleftarrows \text{glycogen}$$

Embden[2] had previously shown that d-lactic acid arises through the artificial perfusion of a liver which is rich in glycogen. He also stated that lactic acid might pass again into glucose thereby establishing a kind of chemical circulation of carbohydrate in the body.

Fürth[3] has confirmed this work by demonstrating that the quantity of lactic acid eliminated in phosphorus poisoning is increased after administering glucose. He further showed that the lactic acid elimination which occurs after cooling rabbits is increased if carbohydrate be ingested, and is prevented if the animal be freed from carbohydrate by means of adrenalin. He, therefore, concluded that lactic acid unquestionably arose from glucose.

Embden and Isaac[4] find that, in contrast with normal livers, those of depancreatized dogs do not convert glucose into lactic acid on perfusion.

[1] Mandel, A. R., and Lusk, G.: Am. J. Physiol., 1906, **16**, 129.
[2] Embden, G.: Centralbl. f. Physiol., 1904, **18**, 832.
[3] Fürth, O.: Biochem. Z., 1914, **64**, 131; *Ibid.*, p. 156.
[4] Embden, G., and Isaac, S.: Z. physiol. Chem., 1917, **99**, 297.

d-Lactic acid is always found in the normal blood and muscle. Von Fürth[1] states that there are between 350 and 550 milligrams of lactic acid in 100 grams of fresh normal muscle of man, horse, dog, and ox.

Levene has accomplished a large amount of work upon the intermediary metabolism of carbohydrate. He[2] reported that leucocytes suspended in a Henderson phosphate mixture containing glucose induced glycolysis with the formation of d-lactic acid only, and without evidence of oxidation. This work has been confirmed by others,[3] who have shown that glycolysis in the shed blood is nothing more than the conversion of glucose into lactic acid. Oppenheimer[4] reports a rapid formation of d-lactic acid when d-fructose is added to a perfusing fluid and passed through a surviving liver.

Levene and Meyer[5] found further that leucocytes formed lactic acid from d-glucose, d-mannose, and d-galactose, and that kidney tissue caused a formation of lactic acid from d-glucose, d-fructose, and d-mannose.

The reactions which lead to the production of d-lactic acid from the various hexoses necessitate the presence of an intermediate substance, otherwise d-l-lactic acid would frequently be the end-product.

Wohl[6] refers to the fact that methylglyoxal in alkaline solution is convertible into lactic acid. This has been shown to take place in tissue by Dakin[7] and by Neuberg,[8] and to be induced by white blood-cells.[9]

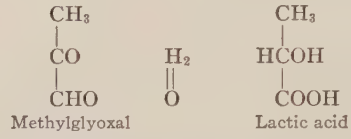
The three trioses, d- and l-glyceric aldehyd and dihydroxyaceton, yield lactic acid when treated with alkali.[10] This suggests the possibility of glyceric aldehyd and dihydroxyaceton being intermediate metabolites of glucose.

The production of methylglyoxal ($CH_3.CO.CHO$ or $CH_2:COH.CHO$) as an intermediary metabolite of sugar metabolism is of theoretic importance as showing by what means the asymmetry of

[1] von Fürth, O.: Biochem. Z., 1915, **69**, 199.
[2] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1912, **11**, 361; 1912, **12**, 265.
[3] Kraske, B.: Biochem. Z., 1912, **45**, 81; Kondo, K.: *Ibid.*, p. 88; von Noorden, K., Jr.: *Ibid.*, p. 94.
[4] Oppenheimer, S.: *Ibid.*, 1912, **45**, 30.
[5] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1913, **14**, 149, and *ibid.*, **15**, p. 65.
[6] Wohl, A.: Biochem. Z., 1907, **5**, 45.
[7] Dakin, H. D., and Dudley, H. W.: J. Biol. Chem., 1913, **14**, 155.
[8] Neuberg, C.: Biochem. Z., 1913, **49**, 502.
[9] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1913, **14**, 551.
[10] Oppenheimer, M.: Biochem. Z, 1912, **45**, 134.

the central carbon atom of a triose like d-l-glyceric aldehyd may be abolished, and then through the determinative influence of living cells be transmuted into a d-compound (Dakin, see p. 232).

It will be shown later that lactic acid appears in the urine in many asphyxial conditions (see p. 577), and the long series of experiments which have been very briefly referred to above have been performed under asphyxial conditions.[1] Only under these circumstances can the Cannizzaro reaction (see p. 232) take place.



Methylglyoxal Lactic acid

The fundamental principles established by the earlier workers have been extended by special researches in specific fields which must now be considered. The details are perhaps burdensome; the truth is elusive. It is easy to write formulae to serve one's purpose. The question is whether the truth is in them. The field is fascinating, with beautiful vistas and many pitfalls.

Lactacidogen.—In 1880 Boehm[2] investigated the behavior of glycogen and lactic acid in a muscle which had undergone rigor mortis under antiseptic conditions. He stated in italics, "In this way it can be shown that lactic acid production in muscle rigor is not at the expense of muscle glycogen." In one experiment a muscle contained 0.71 per cent. of glycogen, both when fresh and 18 hours thereafter, although its lactic acid content rose from 0.22 per cent. to 0.57 per cent. as the result of rigor. This was in anticipation of Embden's work.

Embden, Griesbach, and Schmitz[3] showed that muscle press juice, after short standing at 40° and after addition of $NaHCO_3$, yielded lactic acid and phosphoric acid in nearly molecular equivalent amounts. Hence they concluded that a ferment acted on a hexose phosphoric acid complex. When they added to the press juice the hexose-phosphate prepared by yeast fermentation, that also was converted into lactic acid and inorganic phosphate. Glucose itself was not turned into lactic acid. They found more lactic acid and

[1] Woodyatt, R. T.: Wells's "Chemical Pathology," Philadelphia and London, 4th ed., 1920, p. 642.
[2] Boehm, R.: Pflüger's Arch. gesam. Physiol., 1880, **23**, 44.
[3] Embden, G., Griesbach, W., and Schmitz, E.: Z. physiol. Chem., 1914–15, **93**, 1.

more inorganic phosphate in active than in resting muscle and concluded that the reaction took place in muscular contraction.[1]

Embden, Griesbach, and Laquer[2] prepared an osazone from muscle press juice which was identical with the yeast hexose-diphosphate. Embden and Laquer[3] state that this compound unquestionably exists in the muscle of the frog, dog, and rabbit and is a derivative of *lactacidogen*. Embden and Zimmermann[4] conclude that hexose-diphosphoric acid is lactacidogen itself.

After mechanical work there is a great reduction in the amount of lactacidogen in the muscle while the inorganic phosphate of the muscle increases; and during work there is an increased output of phosphate in the urine. The inorganic phosphate, when liberated, may unite with other glucose to form fresh hexose-phosphate.

Embden[5] concludes that in muscular activity hexose-phosphate is converted into sugar and phosphoric acid, but that only a part of the sugar thus dissociated passes into lactic acid. He considers that the goodly quantity of phosphoric acid liberated is more essential in muscular contraction than is the production of lactic acid. Von Euler[6] confirms Embden's observation that much less lactic acid is formed from lactacidogen than corresponds to the phosphoric acid set free.

In considering Embden's scheme one must remember the recent discoveries of creatin-phosphoric acid (see p. 254), which is believed to yield phosphoric acid in muscular contraction, and of "phosphagen," discovered by Eggleton and Eggleton.[7] Phosphagen is hexose monophosphoric acid which can be separated from frog's gastrocnemius by acids in the cold, and which Embden confounded with inorganic phosphate because he used too strongly acid solutions. The large output of urinary phosphate in sudden great effort is stated to be due to the ready breakdown of this substance into lactic acid and inorganic phosphate. It is stated that phosphagen may be generated from glycogen and phosphoric acid.

The Hill-Meyerhof Theory of Muscular Contraction.—This is not the place to discuss in full the Hill-Meyerhof theory of muscular

[1] Consult Beattie, F., and Milroy, T. H.: J. Physiol., 1926–27, **62**, 174.
[2] Embden, G., Griesbach, W., and Laquer, F.: Z. physiol. Chem., 1914–15, **93**, 124.
[3] Embden, G., and Laquer, F.: *Ibid.*, 1921, **113**, 1.
[4] Embden, G., and Zimmermann, M.: *Ibid.*, 1924, **141**, 225.
[5] Embden, G.: "Handbuch der normalen und pathologischen Physiologie," 1925, **8**, 1, 369.
[6] v. Euler, H., Myrbäck, K., and Karlsson, S.: Z. physiol. Chem., 1925, **143**, 243.
[7] Eggleton, P., and Eggleton, G. P.: J. Physiol., 1927, **63**, 155.

contraction, but there are certain phases of the question which are indispensable in the consideration of carbohydrate metabolism. The origin of the work lay in the discovery by Fletcher and Hopkins[1] that there were only traces of lactic acid in the normal resting frog's muscle, also only traces after a series of muscular contractions which were induced in an atmosphere of oxygen; but that lactic acid appeared in large quantity in the muscle if the contractions were brought about in hydrogen gas under anaerobic conditions. Under the last named conditions carbondioxid was driven out of the muscle on account of the neutralization of bicarbonate by lactic acid.[2] When oxygen was admitted Fletcher and Hopkins noted that the lactic acid in the muscle disappeared, and they ascribed this to its oxidation.

The work of Hill and Meyerhof upon the nature of the chemical and energy reactions in muscle has attracted world-wide attention. The modern conception that the initial heat of the muscle contraction is derived from the breakdown of a precursor into lactic acid was first presented by A. V. Hill[3] before the Physiological Society of Great Britain on February 14, 1914. He said that, of the quantity of lactic acid produced, a large amount "is not oxidized but replaced in its previous position, under the influence and with the energy of the oxidation, either (*a*) of a small part of the lactic acid itself, or (*b*) of some other body. Evidence given elsewhere shows that it must be of some other body. The lactic acid therefore is part of the machine and not part of the fuel."

However, it was accepted later by Hill that a part of the lactic acid was oxidized.

It was the service of Meyerhof[4] to show that the disappearance of lactic acid when oxygen was admitted after a muscle had contracted in hydrogen was largely, if not entirely, due to the reconstruction of lactic acid into glycogen under the influence of the admitted oxygen. In Meyerhof's[5] opinion, printed in the original in italics, the situation was defined as follows: "Genau wie im intakten Muskel wandeln sich unter Oxidation eines Moleküls Milchsäure drei andere anaerob zurück." Meyerhof[6] subsequently changed his opinion and stated

[1] Fletcher, W. M., and Hopkins, F. G.: J. Physiol., 1906–07, **35**, 247.
[2] Fletcher, W. M., and Brown, G. M.: *Ibid.*, 1914, **48**, 177.
[3] Hill, A. V.: Proc. Physiol. Soc., J. Physiol., 1914, **43**, p. x.
[4] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1919, **175**, 82.
[5] Meyerhof, O.: *Ibid.*, 1921, **188**, 114.
[6] Meyerhof, O.: J. Gen. Physiol., 1926–27, **8**, 531.

that Lusk[1] had misunderstood his theory regarding the oxidative restitution of lactic acid into glycogen. He now says "It was not meant that the burning of part of the lactic acid was requisite as the exclusive source of energy for resynthesis of the remaining lactic acid."

According to the Hill-Meyerhof theory (see p. 438), when a muscle contracts, lactic acid is produced anaerobically from glycogen. During the recovery phase the greater part is reconstituted into glycogen. The important point is this, if the restitution is complete, then, in the words of Hill's first paper, lactic acid is part of the machine and not part of the fuel. If it is incomplete and a fasting dog be capable of great muscular effort,[2] then there must be a constant production of sugar from fat to supply the fuel for the restitution process. In my judgment the production of sugar from fat in the animal body is a figment of the imagination (see p. 639). The tenacious hold of the active muscle upon its glycogen supply in fasting and in diabetes indicates that the mechanism, glycogen → lactic acid → glycogen, is not maintained at the expense of the oxidation of lactic acid but rather of fat. In muscular work in phlorhizin diabetes a part of this lactic acid may pass into the blood, be carried to the liver, there synthesized to glucose, and be eliminated as "extra sugar" in the urine. But a second period of muscular work results in no such elimination of "extra sugar," the muscle holding tenaciously what is left of its glycogen (see p. 641). Can one believe that under these circumstances fat passes into glycogen in exactly the quantity necessary to furnish the material of one of the four molecules of lactic acid liberated in muscular contraction so that one may be oxidized and constitute the fuel of the restitution process?

It appears more probable that *lactic acid cannot be oxidized in the body*. It is everywhere the end-product of anaerobic conditions and must be reconstituted into glycogen and then pursue another path of metabolism if it is to be oxidized.

Janssen and Jost[3] find that the intravenous perfusion of dogs with sodium lactate in amounts reaching 1 gm. per kg. of body weight per hour resulted in no increase in the quantity of glycogen in the muscle. They conclude that the liver plays a more important rôle in carbohydrate synthesis than do the muscles.

[1] Lusk, G.: Biochem. Z., 1925, **156**, 334.
[2] Anderson, R. J., and Lusk, G.: J. Biol. Chem., 1917, **32**, 421.
[3] Janssen, S., and Jost, H.: Z. physiol. Chem., 1925, **148**, 41.

Insulin Shock. The Dehepatized Dog.—Two new methods, both of which depend upon the revival of animals suffering from hypoglycemic shock, have been placed in our hands. Such animals are quickly revived if glucose be introduced into their blood, or recovery results if material be given which is oxidized after the fashion of glucose.

It has been discovered by Banting, Best, Collip, Macleod, and Noble[1] that convulsions occurred in the rabbit when after insulin the glucose content of the blood fell to 0.045 per cent..

Mann and Magath[2] completely extirpated the livers of dogs. They write, "One hour after operation the animal usually appears almost normal, and remains so from three to eight hours . . . The onset of the moribund period is usually sudden and the subsequent development of various symptoms typical and rapid." The symptoms and order of their occurrence are: muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitchings, and convulsions. Death ensued within 2 hours after the first signs of muscular weakness. The blood sugar stood at 0.04 per cent. and the muscle glycogen was reduced by one-half at the time the animal became moribund. The amount of glycogen in the muscles is sufficient to restore the normal blood sugar level if it could be released. But it is impossible of rapid conversion into glucose for this purpose. If glucose be injected the muscle glycogen increases therein.

"The effect of the intravenous injection of glucose on an animal dying from the removal of the liver is one of the most remarkable physiologic phenomena we have ever observed. The animal, comatose and perfectly flaccid, apparently unable to contract any muscle except the diaphragm, is restored immediately to a seemingly normal condition by the injection of 0.25 to 0.5 gm. glucose for each kilogram of body weight. We have seen such animals stand 30 seconds after the injection of glucose, walk, respond to call, wag their tails, drink water, and so forth, in less than one minute from the time they had been perfectly flaccid." (Mann and Magath.)

If the blood sugar level be maintained the animal may live for 18 to 24 hours, but it then dies from a second set of symptoms of unknown cause.

[1] Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.: Am. J. Physiol., 1922, **62**, 162.

[2] Mann, F. C., and Magath, T. B.: Arch. Int. Med., 1922, **30**, 73, 171; Am. J. Physiol., 1923, **65**, 403; Bollman, J. L., Mann, F. C., and Magath, T. B.: *Ibid.*, 1925, **74**, 238.

The authors find that besides *glucose*, both *maltose* and *mannose* are effective in reviving the animal, galactose and dextrin are slightly effective. Fructose has no value, signifying perhaps that the liver is necessary for its transformation before utilization. Sucrose and lactose are without value, for they are not oxidized in the body being completely eliminated in the urine after their subcutaneous injection.[1] And possible products of carbohydrate metabolism, such as lactic acid, pyruvic acid, glycerol, ethyl alcohol, and acetic acid, have no power to cause recuperation. Glycin, which requires deamination by the liver to insure its utilization, was not able to restore the dog.

When insulin was given to the dehepatized dog the characteristic deep depression of the blood sugar followed, showing that the liver was not essential to the proper functioning of insulin.

The revival of animals from *insulin shock* has been investigated by Noble and Macleod[2] and by Herring, Irvine, and Macleod[3] with results almost identical with those obtained by Mann. *Glucose* and *mannose* gave complete and positive recovery and were equally effective; *maltose* was more slowly effective; *fructose* and *galactose* gave only partial results, *i.e.*, there was an immediate recovery with quick return of the symptoms. All other substances tried, such as the pentoses, arabinose and xylose, β-glucosan, sodium lactate, and glycerol were of no avail in insulin hypoglycemia.

The results are not in accord with those of Voegtlin, Dunn and Thompson[4] who find that glycerol is very effective in preventing insulin death markedly raising the blood sugar level. They also report that galactose and fructose afford good protection, that d-alanin is as effective as glucose, but that lactic acid is, surprisingly, negative in its action.

That the action of insulin is preferentially upon glucose rather than on fructose was shown by Wierzuchowski,[5] who demonstrated that when either glucose or fructose solutions are injected into dogs intravenously by a continuous Woodyatt pump at the rate of 2 gm. per kilogram of body weight per hour, about 10 per cent. of each sugar escapes in the urine. When insulin is injected with glucose the urine sugar drops to 1 per cent. of that administered. However, when

[1] Voit. F.: Dent. Arch. klin. Med. 1897, **58**, 523.
[2] Noble, E. C., and Macleod, J. J. R.: Am. J. Physiol., 1923, **64**, 547.
[3] Herring, P. T., Irvine, J. C., and Macleod, J. J. R.: Biochem. J., 1924, **18**, 1023.
[4] Voegtlin, C., Dunn, E. R. and Thompson, J. W., Am. J. Physiol, 1924–25, **71**, 574.
[5] Wierzuchowski, M.: J. Biol. Chem., 1926, **68**, 631.

insulin is injected with fructose the elimination of fructose in the urine remains unchanged, though there is a small drop in blood sugar due to the combustion of pre-existing glucose.

There is general unanimity of opinion that there is no significant increase in the lactic acid content of the blood when insulin is administered to a diabetic with high blood sugar or to men or animals which have been given high carbohydrate diets.[1] Only after epinephrin or convulsions does lactic acid pour into the blood (see p. 443).

The behavior of dihydroxyaceton has assumed special importance. Laufberger[2] showed that it was rapidly oxidized by normal rabbits. Its ready combustion in man was first observed by Rabinowitch.[3] Wind[4] found that it was oxidized in neutral phosphate solution by atmospheric oxygen 20 to 30 times as fast as fructose is oxidized under similar circumstances. Campbell and Hepburn[5] have given insulin to a man suffering with severe diabetes and reduced his blood sugar to 0.03 per cent., at which time he was drowsy. The patient was given 50 gm. of dihydroxyaceton. In 10 minutes his condition was improved; in 20 minutes the blood sugar was 0.04 per cent.; in 40 minutes it was 0.056 per cent., the patient apparently normal; and in 50 minutes, with a blood sugar of 0.066 per cent., he was perfectly normal.

Several years ago it was shown by Ringer[6] that dihydroxyaceton was completely convertible into glucose in the body.

Hewitt and Reeves[7] make the important announcement that the insulin hypoglycemia of rabbits and mice is cured by dihydroxyaceton and not by glyceric aldehyd. Therefore glyceric aldehyd does not pass into dihydroxyaceton, and the latter is probably the intermediate in carbohydrate metabolism. Fischler,[8] however, believes that both glyceric aldehyd and dihydroxyaceton have essentially the same curative power as glucose and are apparently its physiological equivalent. Dihydroxyaceton readily passes into glyceric aldehyd in alkaline solutions. The lower products of carbohydrate metabolism,

[1] Tolstoi, E., Loebel, R. O., Levine, S. Z., and Richardson, H. B.: Proc. Soc. Exper. Biol. and Med., 1923–24, **21**, 449; Best, C. H., and Ridout, J. H.: J. Biol. Chem., 1925, **63**, 197; Cori, C. F.: *Ibid.*, p. 253; Collazo, J. A., and Lewicki, J.: Biochem. Z., 1925, **158**, 136.

[2] Laufberger, V.: *Ibid.*, p. 259.

[3] Rabinowitch, I. M.: Canadian Med. Assn. J., 1925, **15**, 374.

[4] Wind, F.: Biochem. Z., 1925, **159**, 58.

[5] Campbell, W. R., and Hepburn, J.: J. Biol. Chem., 1926, **68**, 575.

[6] Ringer, A. I., and Frankel, E. M.: *Ibid.*, 1914, **18**, 233.

[7] Hewitt, J. A., and Reeves, H. G.: Lancet, 1926, **2**, 703.

[8] Fischler, F.: Z. physiol. Chem., 1927, **165**, 68.

lactic and pyruvic acids, acetaldehyd, glycol, and glycolaldehyd did not cause recovery.

Kermack, Lambie, and Slater[1] find that the recovery of animals from insulin shock by dihydroxyaceton does not raise the blood sugar rapidly, and they believe that the material is probably oxidized directly. This is confirmed by Silberstein, Freud, and Révész,[2] who find that the blood sugar values may not rise at all and therefore that it is the combustion of the dihydroxyaceton which matters. Acetaldehyd has no recuperative power. Kermack, Lambie, and Slater report that neither methylglyoxal nor sodium pyruvate can prevent insulin convulsions and that both manifest a toxic action (see also Fischler[3]). Neither Ringer nor Dakin found pyruvate to be toxic. Since dihydroxyaceton and glucose are of equal value in restoring the animal to the normal state, Kermack *et al* suggest the hypothesis that an equilibrium exists in the body between dihydroxyaceton and glucose but that in the absence of insulin, as in diabetes, the tendency of dihydroxyaceton would be toward glucose (formula on p. 348).

Incidentally it may be remarked that if dihydroxyaceton is the normal intermediate of carbohydrate metabolism it could readily yield glycol aldehyd which Shaffer shows is strongly ketolytic. It is less readily evident how glycolaldehyd could form fat.

$$CH_2OH—CO—CH_2OH + O_2 \rightarrow CH_2OHCHO + CO_2 + H_2O$$

Another detail of importance is the behavior of *hexose phosphate.* Marks and Morgan[4] make the surprising announcement that neither mono- nor hexose diphosphate relieves insulin hypoglycemia in rabbits and mice. That the diphosphate may be transformed into glucose was shown by Fürth and Marian,[5] who gave 40 gm. (= 16.8 gm. glucose) to a phlorhizinized dog. On the days before and after giving the material the D : N ratios were 3.08 and 2.97. On the day of the ingestion the D : N was 5.04. The nitrogen in the urine fell, indicating a partial oxidation of the material, and the extra sugar was 10.3 gm. or 60 per cent. of the quantity in the hexose phosphate ingested.

If hexose phosphate will not restore the animal in insulin hypoglycemia the indications are that it belongs to that mechanism in the

[1] Kermack, W. O., Lambie, C. G., and Slater, R. H.: Biochem. J., 1926, **20,** 486; 1927, **21,** 40.
[2] Silberstein, F., Freud, J., and Révész, T.: Biochem. Z., 1927, **181,** 327.
[3] Fischler, F.: Z. physiol. Chem., 1927, **165,** 68.
[4] Marks, H. P., and Morgan, W. T. J.: Biochem. J., 1927, **21,** 530.
[5] Fürth, O., and Marian, J.: Biochem. Z., 1926, **167,** 123.

muscle which, as we have seen, yields its glycogen only with difficulty for the replenishment of the blood sugar. In support of this Schmitz and Chrometzka[1] report that muscle tissue alone has the power to split hexose diphosphate.

SUMMARY

Of all the intermediary substances which modern research holds to be products of alcoholic fermentation of carbohydrate glycerol alone appears to fulfill the physiological requirements of an animal suffering from urgent carbohydrate want. Pyruvic acid, the cornerstone of Neuberg's scheme, is reported as of no avail; likewise methylglyoxal. It is possible, however, that administration of this substance results in its immediate conversion into lactic acid (see p. 232). Lactic acid, often held to be the cardinal oxidative fragment of glucose, avails nought. Acetaldehyd is not only an anesthetic, but it will not revive insulinized animals. This is as would be expected, since it is not convertible into glucose (see p. 662). It seems highly probable that Neuberg's scheme of alcoholic fermentation is entirely correct; it seems uncertain that it has much application to the state of affairs in the animal body. The reports by many authors of traces of acetaldehyd in urine of both normal and diabetic persons and in the tissues of animals do not carry conviction that acetaldehyd, broken from pyruvic acid, is a normal product of carbohydrate metabolism in the animal body.[2]

Levene and Meyer[3] find that leucocytes and kidney tissue will not cause the cleavage of pyruvic acid into acetaldehyd and carbon dioxid nor oxidize it either, so that when one comes to consider the ultimate fate of glucose in the organism the question is beset with difficulties.

There are, however, many indications that acetaldehyd is one of the intermediary metabolites by some other pathway. Rabinowitch,[4] in a recent paper, confirms the easy oxidation of dihydroxyaceton in normal and diabetic individuals and further extends the evidence presented that it need not pass into glucose before oxidation. Since it revives animals from hypoglycemic shock, it appears to be the equivalent of glucose in metabolism and may perhaps be the

[1] Schmitz, E., and Chrometzka, F.: Z. physiol. Chem., 1925, **144**, 196.

[2] For contrary opinion read: Neuberg, C., and Gottschalk, A.: Biochem. Z., 1924, **151**, 167.

[3] Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1914, **17**, 443.

[4] Rabinowitch, I. M.: *Ibid.*, 1927, **75**, 45.

earliest product of its metabolism. It may pass with ease either by oxidation into glycolaldehyd or through the intervention of water into acetaldehyd (see p. 349).

BEHAVIOR OF ISOLATED TISSUES

Meyerhof[1] obtained a respiratory quotient of unity in the extirpated muscle of the frog and attributed it to the oxidation of lactic acid.

Warburg, Posener, and Negelein[2] showed that carcinoma cells and brain tissue were able to convert large quantities of glucose into lactic acid. Warburg[3] reported that Rous's chicken sarcoma formed 12 per cent. of its weight of lactic acid in one hour without oxygen and 8 per cent. when oxygen was allowed, indicating a small and insufficient respiration.

Loebel,[4] working in Meyerhof's laboratory, examined the metabolism of freshly extirpated thin sections of the cerebral cortex of the rat. Such brain sections do not convert their own carbohydrate into lactic acid. But if glucose is given anaerobically much lactic acid is formed, whereas if fructose is offered to the cells no lactic acid is produced. However, both glucose and fructose are readily oxidized by brain tissue in the Warburg apparatus, as is evidenced by respiratory quotients of 0.99 and 0.92. Loebel concludes that lactic acid is not an intermediate metabolite of fructose and thinks it possible that lactic acid, once formed, must first pass back into glucose before it is oxidized.

Holmes and Holmes[5] find that the brain tissue of depancreatized cats maintains its glycolytic power of changing glucose into lactic acid and that aeration leads to the removal of part of the lactic acid.

Loebel and Hickling[6] have determined the respiratory quotient of testicular tissue in the rat by the manometric methods of Warburg. The fine strands of tubules were provided with an adequate oxygen supply in a buffered Ringer solution both with and without the addition of sodium lactate. With no lactate present the oxygen consumption is low and falls rapidly. With lactate the oxygen consumption is greater, is constant for several hours, and the respiratory

[1] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1919, **175**, 20.
[2] Warburg, O., Posener, K., and Negelein, E.: Biochem. Z., 1924, **152**, 309.
[3] Warburg, O.: *Ibid.*, 1925, **160**, 307.
[4] Loebel, R. O.: *Ibid.*, 1925, **161**, 219.
[5] Holmes, B. E., and Holmes, E. G.: Biochem. J., 1927, **21**, 412.
[6] Loebel, R. O., and Hickling, R. A.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1927, **81**, 494.

quotient rises. There is a synthetic production of carbohydrate in greater amount than corresponds to the lactic acid removed by oxidation. Whether the lactic acid is directly oxidized or first passes into carbohydrate before oxidation cannot be definitely stated on the basis of these experiments.

Richardson, Loebel, and Shorr[1] have made interesting observations on the respiratory quotients of excised renal tissue of the rat. Their data include observations on well-nourished as well as fasting rat tissue with or without glucose added to the buffered Ringer solution. The lowest respiratory quotient observed in fasting was 0.705, or the theoretical quotient for fat; the highest (with glucose) was 0.95, or nearly that of pure carbohydrate combustion. No quotient was obtained which was above unity, which would indicate the production of fat from carbohydrate, nor below 0.7, which would betoken the transformation of fat into carbohydrate. There is a rise in the respiratory quotient when glucose in solution is offered to the living tissue for oxidation. Duplicate analyses of the respiratory quotients observed for excised renal tissue by the Warburg-Barcroft manometer method showed that the average error was only ± 0.014. Unpublished experiments of these workers show that isolated muscle tissue taken from a diabetic animal manifests the theoretic diabetic respiratory quotient of 0.69, a value which is unchanged if glucose is placed in the surrounding medium. In these experiments the workers of the Russell Sage Institute of Pathology in Bellevue Hospital demonstrate that the laws of metabolism in excised animal tissues are not different from those deducible from the metabolism of a human being as revealed by the Sage respiration calorimeter in the same hospital.

Büchner and Grafe[2] have studied the respiratory metabolism of kidney, liver, spleen, and muscle in glucose-Ringer solution with and without insulin and conclude that insulin increases the oxygen consumption and raises the respiratory quotient in all the organs of the body. A comparatively new and very interesting field is opened by these experiments.

Ahlgren,[3] using the methylene blue method, finds that the reduction of methylene blue is not accelerated if glucose alone be added to

[1] Richardson, H. B., Loebel, R. O., and Shorr, E.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 243.
[2] Büchner, S., and Grafe, E.: Deut. Arch. klin. Med., 1924, **144**, 67.
[3] Ahlgren, G.: Skan. Arch. Physiol., 1926, **47**, Suppl., 271, 275.

frog's washed muscle tissue, nor if insulin alone is so administered. But if insulin and glucose in a nearly neutral phosphate solution are introduced together into the system there is a decided acceleration in the reaction. Glucose and insulin do not react without the presence of a tissue element, *glucomutin*, which Ahlgren believes is essential for the transformation of the α-β-glucose of the blood into an oxidizable form which he calls x-glucose. Epinephrin and *prior* addition of phlorhizin to the tissue inhibits the reaction, glucose-insulin-glucomutin. Levulose will not react as glucose does.

THE RATE OF TRANSFORMATION OF FRUCTOSE, AND GALACTOSE INTO GLUCOSE

Following the idea of Csonka which proved that alanin and glycin were absorbed, deaminized, and eliminated as extra sugar in the urine of a phlorhizinized dog as quickly as an equal amount of glucose itself would have been had it been given the animal (see

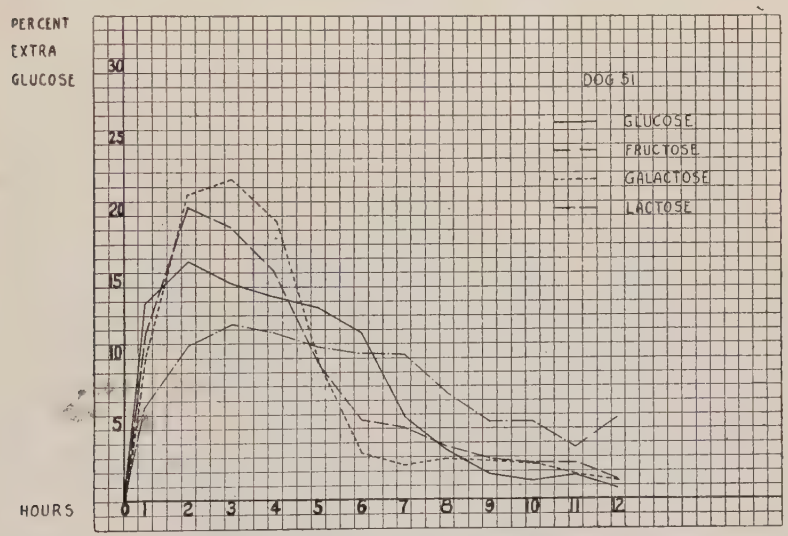


Fig. 23.—Curve showing in per cent. the elimination of "extra sugar" in the phlorhizinized dog after giving 16 gm. of glucose, fructose, galactose, lactose (Deuel and Chambers).

p. 294), Deuel and Chambers[1] gave 16 gm. of glucose, fructose, and galactose to fasting phlorhizinized dogs and found that the rates of hourly elimination of extra glucose were almost identical with each variety of sugar. This appears in the accompanying chart.

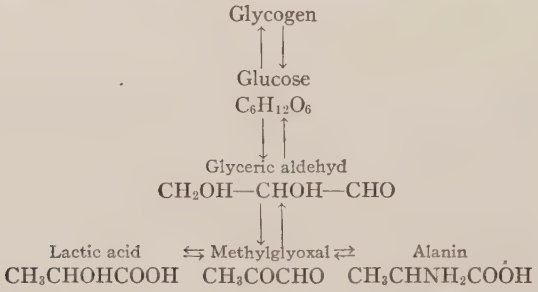
[1] Deuel, H. J., Jr., and Chambers, W. H.: J. Biol. Chem., 1925, **65**, 7.

All of the ingested glucose was eliminated in 5 hours. Of fructose, 95 per cent. was converted into glucose and was nearly all eliminated in 5 hours. Galactose followed closely the same curve and 88 per cent. was converted into glucose and eliminated as extra sugar. It is manifest that in diabetes these sugars undergo a rapid transmutation into glucose, the sugar of the blood.

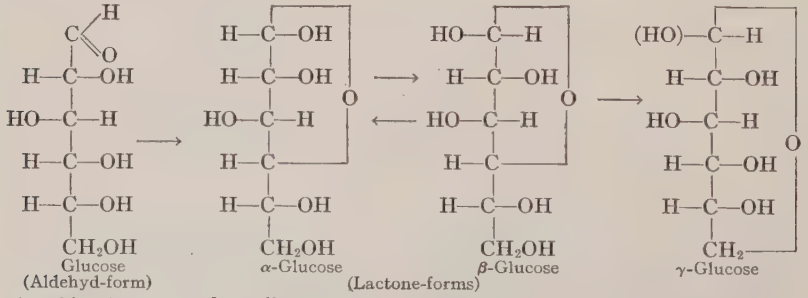
Lactose, which probably undergoes bacterial fermentation in the dog's intestine (see p. 381), was only slowly converted into extra glucose, and only 50 per cent. of the sugar given was recovered.

THEORETICAL

In 1913 Dakin and Dudley,[1] after considering all the evidence at hand, presented "the construction of a crude scheme aiming at the representation of the biological interconversions of alanin, lactic acid, methylglyoxal, glyceric aldehyd and glucose" (details, pp. 232, 331).



The breakdown of glucose in the body has been thought to be preceded by its conversion into a highly reactive but purely theoretical form called γ-glucose. The following path is given by Pringsheim.[2] The last formula, that of γ-glucose, is unknown but is assumed by Pringsheim.



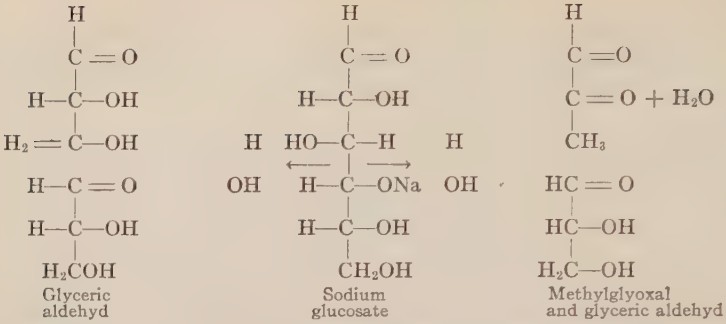
[1] Dakin, H. D., and Dudley, H. W.: XVIIth Internat. Congress Med., London, Subsection IIIa, 1913, p. 105.

[2] Pringsheim, H.: Biochem. Z., 1925, **156**, 109.

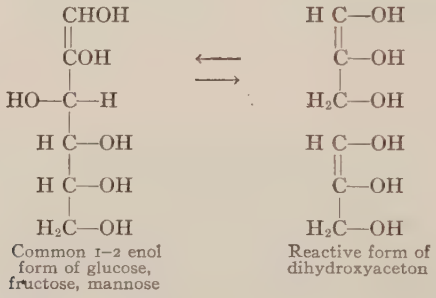
The existence of γ-glucose has been vigorously affirmed and denied. It does not seem worth while to burden this book with the extensive literature on the subject.

A recent article by Toenniessen and Fischer[1] relates how they have mixed muscle pulp and pancreas pulp together, as well as the united extracts of the two organs, and have found that added hexose phosphate is converted into methylglyoxal, but that glycogen and glucose are not thus transformed. It will be remembered that pancreas contains the anti-glyoxalase of Dakin which prevents the transformation of methylglyoxal into lactic acid. Their interpretation of carbohydrate breakdown is as follows:

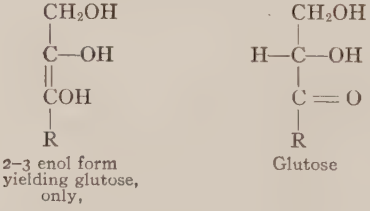
Glycogen
γ-Glucose ← — — —



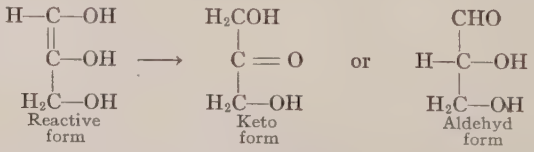
If one considers the hypothesis of Kermack, Lambie, and Slater (see p. 341) that an equilibrium exists between dihydroxyaceton and glucose in the body, then one may draw the following picture of the event:



The 2-3 enol form is not the pathway for it yields glutose, which, when given to a dog, is completely eliminated in the urine and which is not convertible into glucose by the animal.[1]

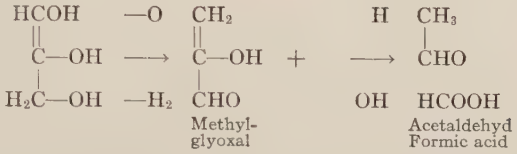


The reactive form of dihydroxyaceton is readily convertible into its keto form or into glyceric aldehyd.



[1] Benedict, E. M., Dakin, H. D., and West, R.: J. Biol. Chem., 1926, **68**, 1.

What now may happen to these fragments is far from certain. The oxidation of one carbon atom of dihydroxyaceton might yield glycolaldehyd (formula on p. 341) which, as we have seen, is strongly ketolytic. The withdrawal of water leaves methylglyoxal, and this reacting again with water may be transformed into acetaldehyd and formic acid.



Given aërobic conditions, acetaldehyd would be immediately oxidized to acetic acid. Under *anaerobic* conditions methylglyoxal is converted into lactic acid as follows:

Lactic acid must first be converted into glucose before it can be oxidized. If anaerobic conditions were present and acetaldehyd were produced, this would at once be converted into ethyl alcohol as in alcoholic fermentation. By the mechanism described Prohibition is automatically enforced in the community of the cells.

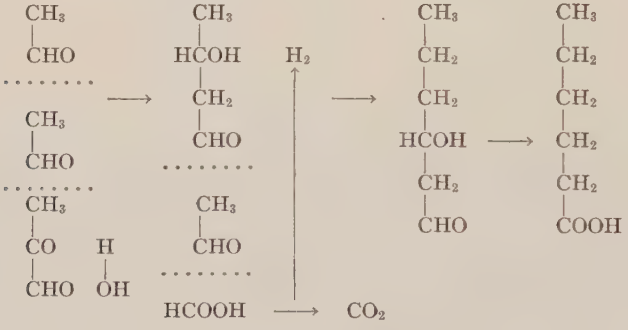
This theory of Lusk has been subjected to a sympathetic and critical analysis by Miss Whetham.[1]

Some theoretical difficulties arise if one assumes acetaldehyd to be an intermediate of carbohydrate. Shaffer shows that it is not ketolytic *in vitro* (see p. 668). Although it is an anesthetic, yet it must arise in extremely small quantities in a unit of time and therefore have a negligible effect. For example, a hog weighing 13 kg. may produce 1.5 mg. of fat from carbohydrate per second and yet lay down in its body 125 gm. of fat per day, or nearly 1 per cent. of its body weight (see p. 398). It is extraordinarily difficult to seize upon the intermediary metabolites involved in this reaction. On the other hand, an athlete may produce 4 gm. of lactic acid in one second according to Hill (see p. 442), and that is why it is possible to find some of it which has diffused from the muscles into the blood.

[1] Whetham, M. D.: Australian J. Exper. Biol. and Med. Sc., 1927, **4**, 35.

That normal urine contains 0.3 to 0.6 mg. per liter of acetaldehyd[1] carries no conviction that it is of importance as a metabolite of carbohydrate. Briggs[2] finds that the administration of alcohol or acetaldehyd to rabbits causes a larger elimination of acetaldehyd in the respiration than in the urine. Since he could not detect any acetaldehyd either in the expired air or in the urine of a rabbit after administering pyruvic acid, he concluded that acetaldehyd was not an intermediary metabolite of carbohydrate metabolism.

Whatever may be the facts of the case, it is easier to conceive of the conversion of acetaldehyd into fat when carbohydrate is given in excess than it is to portray the conversion of glycolaldehyd into fat. Magnus-Levy, in Hofmeister's laboratory, was the first to suggest that the formation of fat was due to the condensation of aldehyd molecules (for Neuberg's scheme see p. 329). The process may thus be crudely pictured:



If at any time the aldehyd radicle at the end of the chain becomes oxidized, the fatty acid is completed and the process of addition terminates. In this fashion, through condensation of acetaldehyd radicles split from methylglyoxal, fatty acids with even numbers of carbon atoms might be synthesized from carbohydrate in the animal organism.

Written in its simplest form the production of palmitic acid from glucose would appear as follows:

$$4C_6H_{12}O_6 = C_{16}H_{32}O_2 + 2HCOOH + 6CO_2 + 6H_2O$$

The end-result is one of carbon dioxid cleavage, just as in the case of the alcoholic fermentation of pyruvic acid induced by yeast cells.

[1] Stepp, W., and Feulgen, R.: Z. physiol. Chem., 1922, **119**, 72.
[2] Briggs, A. P.: J. Biol. Chem., 1926–27, **71**, 67.

The extent to which phosphate plays a part in the normal metabolism of carbohydrate, outside the muscle mechanism, is difficult to determine, but is probably of great importance. Greenwald[1] has found that the principal soluble phosphate of the red blood corpuscle is diphosphoglyceric acid. It is quite possible that such compounds play a part in the intermediary metabolism of carbohydrate.[2]

The various sugars diffuse rapidly in the body. Thus when milk-sugar, which cannot be oxidized by the organism, is introduced intravenously into a dog, after half an hour 75 per cent. of the quantity present in the animal is found in the tissues and only 25 per cent. in the blood.[3] The entrance of glucose into the cells by diffusion is accelerated by increasing their temperature.[4]

[1] Greenwald, I.: J. Biol. Chem., 1916, **25,** 431.
[2] Jost, H.: Z. physiol. Chem., 1927, **165,** 171.
[3] Schwarz, D., and Pulay, E.: Z. exper. Path. u. Therap., 1915, **17,** 383.
[4] Masing, E.: Pflüger's Arch. gesam. Physiol., 1914, **156,** 401.

CHAPTER XV

THE INFLUENCE OF THE INGESTION OF CARBOHYDRATE (Continued)

PART II—THE INFLUENCE OF CARBOHYDRATE ON PROTEIN METABOLISM AND PROTEIN RETENTION

Among scientific articles there are to be found not a few wherein the logic and mathematics are faultless but which for all that are worthless, because the assumptions and hypotheses upon which the faultless logic and mathematics rest, do not correspond to actuality. In this most important respect the work of Willard Gibbs is free from error.—Wilhelm Ostwald.

At the suggestion of Voit, who believed that the sudden withdrawal of carbohydrate from the food would increase protein metabolism and would explain the high tissue waste in diabetes, Lusk[1] established himself in nitrogen equilibrium at two different levels. Withdrawal of 350 grams of carbohydrate from the diet increased the protein metabolism as appears below. The losses of body nitrogen are greater for the second day of change in the diet than for the first, since the metabolism at first remains under the influence of an ample glycogen supply which is available as a source of carbohydrate fuel (see p. 78).

INFLUENCE OF CARBOHYDRATE WITHDRAWAL ON PROTEIN METABOLISM

Exp. No.	Days of Experimentation	Food		Excreta N Gm. per Day	± N to Body Gm. per Day	Remarks
		Calories	N Gm. per Day			
I	1, 2, 3	2953	20.55	19.84	+0.71	With carbohydrate.
	1	1078	20.55	23.78	−3.23	Without carbohydrate.
	2, 3	1078	20.55	27.00	−6.45	Without carbohydrate.
II	2	2490	9 23	13.08	−3.85	With carbohydrate.
	1	615	9.23	13.27	−4.04	Without carbohydrate.
	2	615	9.25	17.18	−7.95	Without carbohydrate.

These results may be compared with the later results of Thomas (see p. 189), who showed that protein containing 18.4 grams of nitrogen when given to a man did not maintain the body in nitrogen equilibrium when no carbohydrate was administered.

[1] Lusk, G.: Zeitschrift für Biologie, 1890, **27**, 459.

Tallqvist[1] found that *partial* replacement of carbohydrate by fat in the diet may have no influence or only a transitory one upon the amount of protein metabolized. Thus, after establishing nitrogen equilibrium in man with a diet containing about 16 grams of nitrogen, 10 per cent. of the calories being in protein and 90 per cent. in carbohydrate, he replaced one-third of the carbohydrate calories with an isodynamic quantity of fat and obtained nitrogen equilibrium on the third day of the diet. This is of value in practical dietetics.

Zeller[2] gave to a man a daily diet which contained very little protein and between 2700 and 3300 calories divided into different percentages of carbohydrate and fat. The protein metabolism of the body was not significantly altered until less than 10 per cent. of the total calories were given in the form of carbohydrate, *i.e.*, butter, 360 grams; sugar, 70 grams; sauerkraut, 300 grams; tomatoes, 100 grams, containing 3300 calories. At this juncture, when, as Zeller notes, one molecule of monosaccharid is present for two of fat in the diet, aceton appeared in the urine in traces. When 5 per cent. of the calories were given in carbohydrate, aceton appeared abundantly in the urine, and when the whole of the diet consisted of fat calories there was a still higher aceton excretion, with an increasing ammonia production to neutralize the acid formed and the patient complained of weakness and discomfort.

The following table epitomizes the results obtained:

Food			Urine N Grams	Urine N per 100 Grams N in Body Grams
N Grams	Calories in Per Cent.			
	Carbohydrate	Fat		
3.43	100	0	5.18	0.16
3.21	75	25	5.75	0.18
3.27	50	50	5.60	0.17
3.88	25	75	4.82	0.15
0.87	10	90	5.04	0.16
0.86	5	95	6.02	0.20
1.41	0	100	6.90	0.24
3.43	100	0	4.85	0.15

If two molecules of fat are oxidized in the presence of one molecule of glucose (which assumes that the 3300 calories contained in the diet were liberated in metabolism), then one molecule of fat would be oxidized in the presence of one dissociated triose molecule. Each

[1] Tallqvist, T. W.: Arch. f. Hyg., 1902, 41, 177.
[2] Zeller, H.: Arch. f. Physiol., 1914, p. 213.

molecule of fat is made up of one molecule of glycerol and three of fatty acid. Since glycerol is convertible into a triose, it is apparent that from glycerol and ingested sugar two molecules of triose are available for simultaneous oxidation when three of fatty acid are burned. Besides this, a small number of triose molecules may be derived from protein metabolized and another quota from stored glycogen. It appears from this analysis *possible* that in the normal combustion of fat each molecule of β-oxybutyric acid, which is the end-product of the oxidation of each molecule of fatty acid, requires the presence of a triose molecule. Under these conditions the oxidation of fat would take place without acidosis and without increasing the metabolism of protein. This analysis of the situation has led to a large amount of valuable work upon the subject which had best be treated in the chapter on Diabetes.

It may be noted that when protein is given in large quantity with fat the acidosis does not appear. This is understandable in view of the production of glucose from protein.

A clear-cut experiment by Cathcart[1] shows the characteristic influence of small amounts of carbohydrate, when added to a diet of fat, upon the protein metabolism of the time.

THE INFLUENCE OF FAT AND CARBOHYDRATE ON THE NITROGEN DISTRIBUTION IN THE URINE

(Nitrogen metabolism on 3d day of diet)

Diet (3000–3100 Cals.)	CH Cals. in Per Cent.	Nitrogen in Urine, in Gm.				
		Total	Urea	Ammonia	Creatinin	Uric Acid
323 gm. olive oil.....	0	14.2	10.4	1.13	0.59	0.029
310 " oil + 30 gm. glucose.....	3.8	10.2	6.6	0.58	0.60	0.066
297 " " + 60 " "	7.5	8.6	5.9	0.38	0.50	0.108
279 " " + 100 " "	12.8	7.1	4.8	0.18	0.54	0.145
257 " " + 150 " "	19.0	7.4	5.0	0.16	0.56	0.143

The constancy of the creatinin output is in marked contrast to the reduction in the urea plus ammonia nitrogen. There is a striking reduction in the acid output as measured by the ammonia eliminated.

A significant fact is that when the body changes from a carbohydrate diet to one of fat or protein there is a considerable loss of water and *vice versa*. This was first noted by William Stark in 1769 who records an extraordinary gain in weight of 8 lb. in 5 days after changing his dietary from meat to flour. It was also recorded by

[1] Cathcart, E. P.: Biochem. J., 1922, **16**, 747.

Bischoff and Voit,[1] who gave bread to a dog for forty-one days and witnessed a loss in body weight of 531 grams, although if the nitrogen elimination of the period had been all attributed to muscle breakdown the loss in body weight should have been over 3700 grams. Then when 1800 grams of meat were given in quantity sufficient to cause protein deposit, the weight of the animal fell 310 grams on the first day of this diet.

The phenomenon is also described in man by Benedict and Milner.[2] The experimental period lasted six days, mechanical work was performed daily, and isodynamic quantities of food, which were somewhat under the needs of the body, were ingested. During the first three days 66 per cent. of the energy in the food was contained in carbohydrates, and during the last three days 67 per cent. of the energy was in the form of fat. The following changes were noted:

	Carbohydrate Diet	Fat Diet
Daily change water content of body, grams	+165	−906
Daily change in body weight, grams	+ 61	−914

A loss of body glycogen is, therefore, associated with a loss of body weight in the form of water.

THE WEAR AND TEAR QUOTA OF PROTEIN METABOLISM

If carbohydrates be ingested alone, immediately after starvation, the protein metabolism may fall below the starvation amount.

This higher protein-sparing property gives to dogs fed on carbohydrates alone a longer lease of life than is granted to those fed on fat alone, although the ultimate outcome is the same.

Rubner[3] first called attention to the fact that the protein metabolism of the fasting dog could be reduced to 4 per cent. of the total calories needed if carbohydrate were provided. In his "Energiegesetze"[4] he published the following table of results obtained with a dog:

	Urine N Gm.
Hunger	1.92
"	1.82
Cane sugar, 85 gm.	0.91
" " 110 "	0.72
" " 110 "	0.56
" " 120 "	0.53

[1] Bischoff, T. L. W., and Voit, C.: "Die Gesetze der Ernährung des Fleischfressers," Leipzig and Heidelberg, 1860, pp. 211 and 214.

[2] Benedict, F. G., and Milner, R. D.: U. S. Dept. of Agriculture, Office of Experiment Stations, 1907, Bull. 175, p. 224.

[3] Rubner, M.: Z. f. Biol., 1883, **19**, 391.

[4] Rubner, M.: "Die Gesetze des Energieverbrauchs bei der Ernährung," Leipzig and Vienna, 1902, p. 341.

The physiological nitrogen minimum evidently was intimately associated with carbohydrate metabolism. This minimum of protein metabolism Rubner[1] has called the *"wear and tear" quota of protein metabolism.*

The protein metabolism may be reduced to one-third the fasting value, a result also obtained by Landergren[2] and by Folin[3] in man. Cathcart[4] gave a man who had been fasting fourteen days a diet of cream (300 c.c.) and starch (400 grams). The nitrogen excretion in the urine was as follows:

	Total N Gm.	Urea N Gm.
Day 14 of starvation	7.78	5.99
" 1 on cream-starch diet	7.43	5.80
" 2 " "	3.58	2.29
" 3 " "	2.84	1.76

The absence of a fall in protein metabolism on the first day is probably to be explained by assuming a large deposit of glycogen within the body at the expense of the starch ingested (see p. 376). On the third day of the diet the protein metabolism had fallen to one-third that observed in fasting (see p. 365).

The sparing influence of carbohydrate oxidation upon protein metabolism has been beautifully illustrated by Landergren.[5] Diets containing carbohydrates and fats, but scarcely any nitrogen (about one gram daily), were given to men and the protein metabolism noted. This condition is called that of *specific nitrogen hunger.* After four days' administration of such a diet the urinary nitrogen may be reduced to less than 4 grams.

In one experiment in which this was accomplished carbohydrates were entirely replaced by fat, with the result that protein metabolism rose to the amount found in starvation (about 10 grams). It has already (p. 309) been explained that ingestion of fat alone will not reduce protein metabolism below that of starvation. The experiment is as follows:

Carbohydrate Period Diet = 45.2 Cal. per Kg. Gm. N in Urine		Fat Period Diet = 43.7 Cal. per Kg. Gm. N in Urine	
Day 0	12.76*	Day 5	4.28
" 1		" 6	8.86
" 2		" 7	9.64
" 3			
" 4	3.76		

* Ordinary diet.

[1] Rubner, M.: Arch. f. Hyg., 1908, **66,** 45.
[2] Landergren, E.: Skan. Arch. Physiol., 1903, **14,** 112.
[3] Folin, O.: Am. J. Physiol., 1905, **13,** 45.
[4] Cathcart, E. P.: Biochem. Z., 1907, **6,** 109.
[5] Landergren, E.: *Loc. cit.*

On day 5, the first of the fat diet, it is evident that the protein metabolism was affected by the use of the glycogen supply of the body, an influence which became negligible on the second and third days of the fat diet (p. 78).

Landergren gives the following results in various cases of specific nitrogen hunger, showing the nitrogen in the urine before the diet and after four days thereof:

	II	III	IV	V
N in urine (ordinary diet), gm.	12.76	11.87	13.7	15.2
N in urine (specific N hunger), gm.	3.76	3.95	3.04	4.2
Calories in diet per kg.	45.2	37.8	45.0	38.4

This reduction of protein metabolism to 4 grams on the fourth day was brought about by the following diets in the different cases:

II. 750 g. carbohydrates. = 45.2 cal. per kg.
III. 300 g. carbohydrates + 150 g. fat. = 37.8 " "
V. 380 g. carbohydrates + 150 g. fat. = 38.4 " "

A diet containing half its calories in carbohydrates and half in fat has therefore the same protein protecting power as one made up of carbohydrates alone. This demonstrates the rationality of a mixture of the non-nitrogenous food-stuffs.

The experiments of Karl Thomas have shown the prolonged influence of a previous high protein diet upon the nitrogen output in the urine of man. A starch-cream diet had reduced the urinary nitrogen elimination to 2.2 grams daily. Then, during four days, 76, 87, 85, and 71 grams of nitrogen were given in the diet. The nitrogen retention in the body for the first four days was +43, +25, +8, and −10 grams, a total of +66 grams. This stored protein was by no means as rapidly demolished in the body as it was added to it. This appears in the third column of the following table:

THE INFLUENCE OF PREVIOUS PROTEIN INGESTION UPON THE EXCRETION OF NITROGEN IN GRAMS IN MAN WHEN A DIET OF FAT AND CARBOHYDRATE IS ADMINISTERED

		Landergren[1]	Kinberg[2]	Thomas[3]
Last normal day		12.8	25.2	77.7
Specific N hunger day	1	8.9	18.3	28.3
	2	5.2	14.5	10.7
	3	4.3	11.6	5.1
	4	3.8	9.1	5.2
	5	....	8.0	4.7
	6	....	7.3	4.2
	7	....	5.6	3.9
	19	....	....	2.2
Meat (2.9 gm. N)	20	....	....	2.2

[1] Landergren, E.: *Loc. cit.* [2] Kinberg, G.: Skan. Arch. Physiol., 1911, **25**, 291.
[3] Thomas, K.: Arch. f. Physiol., 1910, Suppl., p. 249.

In the experiment above noted upon Thomas the wear and tear level of 2.2 gm. of urinary nitrogen was established just before and 3 weeks after the 4-day period of high meat ingestion. On the 7 days following this period of meat ingestion the extra nitrogen in the urine over and above the 2.2 gm. of the wear and tear quota was 26.1, 8.5, 2.9, 3.0, 2.5, 2.0, 1.7, or 46.7 gm. in all of the 66 gm. estimated to have been retained. This represents the gradual elimination of "deposit protein," labile protein temporarily stored but not necessarily built up into the living machinery of the cells. Rubner[1] estimates that a kilogram of body weight contains 30 grams of nitrogen. Since the individual investigated by Thomas weighed 73 kilograms, he contained 2190 grams of nitrogen. When given 89 grams of protein nitrogen on a single day this represented 4.5 per cent. of his body's supply. The 66 grams of protein nitrogen stored during the days of liberal protein ingestion, which raised the cells to an optimal condition, represented 3 per cent. of the total protein content. When carbohydrates alone were given this stored protein was only gradually eliminated—there was a *transition period* of constantly diminishing protein waste until a minimum of 2.2 grams of urinary nitrogen (with 0.6 grams in the feces) was found. The urinary nitrogen then represented approximately 1 part in 1000 of protein contained in the organism. This is the lowest wear-and-tear quota of protein metabolism.

Thomas calculated that during the period of minimal wear-and-tear protein metabolism, 0.04 calorie was derived from the metabolism of 1.5 milligrams of protein per kilogram of body weight every hour, while 0.96 calorie was derived from the oxidation of 259 milligrams of glucose. In other words, protein furnished only 4 per cent. of the energy required by a man at rest. Since mechanical work scarcely influences the wear-and-tear quota of protein metabolism (see p. 407), although it largely increases the oxidation of carbohydrate, it is evident that protein may play a very small rôle as a producer of energy for the maintenance of the function of life.

The ability to depress the protein metabolism to the wear and tear level when carbohydrate is given is of value in the interpretation of several diseased conditions and has an important bearing upon metabolism work in the clinic.

[1] Rubner, M.: Arch. f. Hyg., 1908, **66**, 45.

Lauter[1] gives the average normal standard of the wear and tear quota of protein metabolism for a man weighing 70 kg. and adds other data, as follows:

	Man 70 Kg.	Girl 11 Yrs.	Girl 15 Yrs.	Pregnant Woman (9th Month) Age 19 Yrs.
Urine N, gm.	2.66	1.01	2.35	2.09
Urine + feces N, gm.	3.71	1.86	3.28	3.53
Urine N per kg., gm.	0.038	0.035	0.045	0.035
Total N per kg., gm.	0.053	0.046	0.063	0.058
Calories of basal metabolism (Du Bois) in per cent.	.....	2.2	1.6	2.0

On another occasion[2] he reports the following distribution of urinary nitrogen at the wear and tear level of protein metabolism.

	Gm.	Per Cent.
Total N	2.44	
Urea N	1.24	54
NH_3N	0.32	12
Uric acid N	0.10	4
Creatinin N	0.45	19
Rest N	0.30	16

He reports that the nitrogen minimum in carcinoma is 3.76 gm. or twice the normal, whereas a case of Graves' disease with a basal metabolism 85 per cent. above the normal showed, on the last 3 days of carbohydrate diet, 2.15, 2.25, and 2.25 gm. of nitrogen in the urine. This demonstrates that in carcinoma there is a toxic waste of protein and in Graves' disease there is none. Work of similar character had already demonstrated a toxic waste of tissue in typhoid and other fevers (see p. 712).

Deuel[3] partook of a diet free from protein and on the 30th day reduced the total urinary nitrogen to 2.1 gm., a level comparable with that of Thomas. He then received an intravenous injection of 7 mg. thyroxin which wrought havoc with his protein metabolism, the maximum effect, as usual, being observed 7 days after the injection. The protein-free diet was continued until the 55th day, with daily injections of 0.5 to 0.2 mg. of thyroxin, during which time the protein metabolism did not return to the low level of the 30th day.

[1] Lauter, S.: Deut. Arch. klin. Med., 1922, **139**, 46.
[2] Lauter, S., and Jenke, M.: *Ibid.*, 1925, **146**, 323.
[3] Sandiford, I., Sandiford, K., Deuel, H. J., Jr., and Boothby, W. M.: J. Biol. Chem., 1926, **67**, p. xxiv. Many details given in the text are as yet unpublished.

On account of the physical weakness of the subject a low protein diet was administered between the 56th and the 63d days, and then the protein-free diet was resumed. Eleven days thereafter, on the 74th day of the experiment, the urinary nitrogen had fallen to 1.75 gm., of which 33 per cent. was in the form of creatinin and 8 per cent. in uric acid. The creatinin and uric acid outputs remained constant from one end of the experiment to the other. The details may be studied below.

THE WEAR AND TEAR QUOTA OF PROTEIN METABOLISM IN MAN, INCLUDING THE INFLUENCE OF THYROXIN

Day of N-free Diet	Urinary N					Remarks
	Total	NH_3	Urea	Creatinin	Uric Acid	
	Gm.	Gm.	Gm.	Gm.	Gm.	
1	9.73	0.33	7.41	0.59	0.15	Weight = 83.1 kg.
7	4.42	0.24	2.45	0.56	0.17	
14	3.74	0.18	2.13	0.56	0.16	
21	2.72	0.11	1.61	0.56	0.17	
28	2.31	0.10	1.26	0.56	0.14	
30	2.10	0.10	1.14	0.56	0.13	
38	6.12	0.13	4.80	0.57	0.15	Treatment with 7 mg. thyroxin 31st day; low protein diet 56th to 63d day; then N-free diet renewed.
64	3.36	0.15	2.05	0.57	0.14	
73	1.90	0.14	0.84	0.57	0.14	
74	1.75	0.17	0.75	0.56	0.14	Weight = 72.5 kg.

Smith[1] reports the lowest recorded figure for the wear and tear urinary nitrogen of 1.58 gm. on the 24th day of diet free from protein. Of this 35 per cent. was in creatinin, 37 per cent. in urea plus ammonia, 7.7 per cent. in uric acid.

Rubner has given very important definitions. A "*repair quota*" of protein is required in the food in order to replace that lost in the "wear-and-tear" quota. A "*growth quota*" of protein is necessary in addition to a repair quota under the circumstances of multiplication of cells and of developing active protoplasm in the young. Furthermore, an "*improvement quota*" of protein may be necessary in the adult after wasting disease, or after fasting, in order to bring the cells to an optimum of protein condition, thereby improving the welfare of the living organized protein.[2] Under these conditions the

[1] Smith, M.: J. Biol. Chem., 1926, 68, 15.
[2] Rubner, M.: Arch. f. Physiol., 1911, p. 67.

basal metabolism is at a higher level than when the cells are free from this "deposit" (see p. 104) or "improvement" protein. When protein is given in excess so that it is not used for repair nor for growth nor deposit, its constituent amino-acids are deaminized and the residual oxy- or keto-acids are in part converted into glucose, in part into fatty acids, thus yielding fuel to the cells just as would carbohydrate and fat. This fraction of protein Rubner designates as the "*dynamic quota.*"

Thomas[1] administered during frequent intervals small quantities of meat washed free from extractives to the man who had partaken of a starch-cream diet and had reduced his protein metabolism to one represented by a minimum of 2.2 grams of urinary nitrogen daily. Nitrogen equilibrium was nearly achieved after administration of that quantity of protein nitrogen which corresponded to the quantity eliminated in the urine and feces. This is shown below in grams per day:

Day	49	50	51	52	53	54	55
N in diet	0	0	2.89	2.89	2.61	2.61	0
N in urine	2.31	2.16	2.23	2.48	2.56	3.13	3.49
N in feces	0.74	0.73	0.74	0.73	0.74	0.73	0.74
N loss	−3.05	−2.89	−0.08	−0.32	−0.69	−1.25	−4.23

In this experiment the ingestion of the quantity of protein which was the equivalent of the "wear-and-tear" quota was at first nearly sufficient to completely "repair" the tissue. While living upon this low protein diet the mental and muscular power was unchanged.

Rubner[2] finds that a dog, when given a pure fat diet, may be brought near to death when it loses a little more than half of its protein nitrogen. He estimates that a man containing 2100 gm. of protein nitrogen may lose 1128 gm. before death. If the protein metabolism on a pure carbohydrate diet began with 4 gm. N loss and ended with 1.85 gm. daily, then death from this protein-free diet would ensue in 386 days or a little over a year. The danger from protein starvation is therefore much less than from an inadequate supply of food. During the war Rubner privately warned that the maintenance of the caloric value was of greater importance than the maintenance of the protein supply. The protein reserves of the body are relatively enormous.

[1] Thomas, K.: Arch. f. Physiol., 1910, Suppl., p. 249.
[2] Rubner, M.: *Ibid.*, 1919, p. 24.

Though life may be thus prolonged, it should be remembered that the loss of 30 per cent. of body protein is accompanied by marked muscular weakness.

An interesting light is thrown upon the wear and tear quota of protein metabolism by the experiments of Robison.[1] A subject who received a diet of corn-starch, lactose, salt mixture, and agar, together with minimal quantities of lemon juice and cod-liver oil and a small amount of weak tea (2600 to 3000 calories and 0.3 gm. N), ultimately excreted 2.06 gm. urinary nitrogen and 1.13 gm. fecal nitrogen daily. The net loss of body nitrogen was 2.89 gm. Then gelatin was added to the diet during periods of several days. When the gelatin contained 12 gm. of nitrogen per day the total loss of body nitrogen was 2.70 gm., a sparing of only 8 per cent. Fecal nitrogen rose from 1.13 to 1.38 gm. daily, showing almost complete absorption. Yet the sparing of the wear and tear quota of protein metabolism was almost negligible. When gelatin was given during two other periods (4.88 and 7.54 gm. gelatin nitrogen daily) there was a sparing of 12 per cent. in one instance and an extra metabolism of 12 per cent. in the other. The body losses of nitrogen were respectively 2.59 and 3.20 gm. daily.

It appears therefore certain that at the level of the wear and tear of protein metabolism the ingestion of gelatin, a material deficient in cystin, tryptophan, and tyrosin, has scarcely any protective power over the minimal protein metabolism (see p. 190).

It has already been set forth that when benzoic acid is administered to a hog the consequent withdrawal of glycin does not affect the level of the wear and tear metabolism (see p. 225). Thomas[2] has made the remarkable observation that when an animal is at the wear and tear level of protein metabolism administration of brombenzol will not deliver cystein in the form of mercapturic acid. Thomas concludes that free cystein is not liberated under these conditions and that this form of protein metabolism is different from all other forms.

The constant production of creatinin which seems to be unpreventable and which is almost impossible to modify by diet appears to be an essential qualification for the life of the cell, possibly in the interest of a phosphate supply for the oxidation of carbohydrates (see Fiske, p. 254). The tenacious retention of the sulphur containing

[1] Robison, R.: Biochem. J., 1922, **16**, 111.
[2] Thomas, K., and Straczewski, H.: Arch. f. Physiol., 1919, p. 249.

cystein betokens a hold by the tissues upon their supply of glutathion. The large reduction of the urea constituent of the urine without any increase in the total nitrogen elimination after giving benzoate of soda, indicates that the urea formed is a by-product.

As regards the source of the material from which the wear and tear quota is derived, it must be remembered that red blood cells and leucocytes are continually dying and that the muscles are always potentially ready to furnish materials imperatively needed in other parts of the body (milk supply, growth of offspring, etc.).

It is still a point of debate whether the "deposit" or "improvement" protein, which is gradually eliminated under the influence of a high carbohydrate diet, is present as true living protein or whether it represents a special variety of stored protein which is retained in the tissue cells very much as glycogen is retained by them. It has been shown by H. Ellis C. Wilson that when a protein rich in sulphur is ingested the relation between nitrogen and sulphur retained is characteristic of their relative values in muscle and not characteristic of the protein (egg-white) administered (see p. 203). It is believed that the storage takes place largely in the liver.[1] Thus Smith, Belt, and Whipple[2] find that in *plasmapharesis* (see p. 87) (in which there is removal of plasma proteins by hemorrhage accompanied by a proportional replacement of red cells suspended in a protein-free solution) there is a rapid replacement of serum proteins during the first 15 minutes, which indicates that the cells of the body hold a reserve supply. The liver is indicated as the chief source of the material, since a dog with an Eck fistula does not supply these proteins freely.

CARBOHYDRATES AND NITROGEN EQUILIBRIUM

When carbohydrates are given in the diet, it is possible to establish *nitrogen equilibrium* at a much lower level than when protein alone or protein and fat are ingested.

When carbohydrates and protein are ingested together in quantity sufficient for the requirement of the organism, it has been found that, taking the starvation protein metabolism as one, nitrogen equilibrium can be maintained by ingesting one part of protein.[3]

[1] Tichmeneff, N.: Biochem. Z., 1914, **59**, 326; Cahn-Bronner, C. E., *Ibid.*, 1914, **66**, 289.
[2] Smith, H. P., Belt, A. E., and Whipple, G. H.: Am. J. Physiol., 1920, **52**, 54.
[3] Voit, E., and Korkunoff, A.: Z. f. Biol., 1895, **32**, 117.

The work of Sivén,[1] however, was the first indication that nitrogen equilibrium may be maintained at even a lower level than that ordinarily present in starvation. To a somewhat undersized healthy man, weighing 60 kilograms, who normally ate a mixed diet containing 16 grams of nitrogen, was given less and less protein, and an attempt was made to establish nitrogen equilibrium at lower and lower levels. The daily ration was rich in carbohydrates and yielded 2444 calories.

The experiment was divided into four periods of about a week each, which may be summarized as follows:

Length in Days	N in the Food Gm.	Days until N Equilibrium Was Obtained	N Loss before N Equilibrium Was Obtained Gm.	Total N Added to Body Gm.
I, 7	12.69	1	0.53	+9.73
II, 9	10.40	1	0.34	+6.36
III, 6	8.71	at once	....	+4.39
IV, 6	6.26	3	2.09	−0.58

It is apparent that nitrogen equilibrium may be established after ingesting 6.26 grams of nitrogen, although, as has been seen, the elimination during the early days of starvation in man is usually 10 grams. During the first three periods of reduced protein intake, as much as 20.16 grams of protein nitrogen were actually added to the body. In a fifth period nitrogen equilibrium was obtained on the fourth day on a diet containing 4.52 grams of nitrogen.

Petrén[2] has maintained diabetic patients for a month or more in nitrogen equilibrium after giving a diet containing protein N 4 gm., fat 300 gm. and only 50 to 60 gm. of carbohydrate (see p. 663).

Chittenden[3] finds that nitrogen equilibrium may be maintained on a diet containing a very small amount of protein and two-thirds of the body's requirement of energy. The first experiment was on Fletcher and lasted six days. The daily ration contained 7.19 gm. nitrogen + 38.0 gm. fat + 253 gm. carbohydrates = 21.3 calories per kilogram. The excreta contained 6.90 grams of nitrogen daily. On this diet the individual showed "remarkable physical strength and endurance."

Another experiment was performed by Chittenden on himself and lends itself for interesting comparison with the results of the

[1] Sivén, V. O.: Skan. Arch. Physiol., 1900, **10**, 91.

[2] Petrén, K.: J. Biol. Chem. 1924, **61**, 355.

[3] Chittenden, R. H.: "Physiological Economy in Nutrition," New York, 1904, pp. 14, 40.

ingestion of a maintenance ration. The food was principally vegetable. The results may be thus tabulated:

A LOW LEVEL OF NITROGEN EQUILIBRIUM IN NORMAL AND UNDERNUTRITION

Date	Diet		N Excretion Grams	N Balance Grams
	N in Grams	Cal. per Kg.		
March 23	6.79	34.7	6.56	+0.23
March 25	6.88	22.4	6.34	+0.54

Nitrogen equilibrium may therefore be maintained at a low level, even during the state of undernutrition present when 22.4 calories per kilogram are in the daily diet. On a milk diet Rubner[1] found that the ingestion of 2483 grams of milk containing 84 grams of protein and two-thirds the body's requirement of energy resulted in the addition of 6.7 grams of protein to the body daily for three days (see p. 476).

It is a valuable piece of information to know that one may diet an obese patient on a food containing little protein and two-thirds the body's energy requirement without danger of protein loss. The other third of the necessary energy will be furnished by the body's own store of fat. It is not remarkable that the body is capable of great physical effort on such a diet, for a fasting man is also competent in this direction (see p. 77).

The experience of the war time nutrition however has shown that prolonged undernutrition results in a loss of body protein (see p. 173).

The Influence of Gelatin on Protein Metabolism.—In Chapter IX on p. 190 mention was made of the sparing action of gelatin on protein metabolism, and its ingestion was found to prevent about 23 to 37.5 per cent. of the protein loss during starvation. Murlin[2] in an extensive series of experiments has shown that the sparing power of gelatin is greater than this when it is ingested with a mixed diet. He finds that if the quantity of nitrogen eliminated in fasting be taken as one, then nitrogen equilibrium may be maintained in dogs and in man on ingestion of a diet rich in carbohydrates, whether the nitrogen of the diet be protein nitrogen equal to one or whether it contain one-third protein plus two-thirds gelatin nitrogen. This is shown in the following experiment on a man, the results being expressed in averages per day:

[1] Rubner, M.: Z. f. Biol., 1879, **15**, 130.
[2] Murlin, J. R.: Am. J. Physiol., 1907, **19**, 285.

EFFECT OF ADMINISTERING GELATIN IN A MIXED DIET IN MAN
(N elimination on a third day of fasting = 13.23 gm.)

Source of N in Diet	No. of Days	Cal. in Food	Cal. per Kg.	N in Food	N in Excreta	N to Body
				Grams	Grams	Grams
All protein N	3	3208	47	14.25	13.33	+0.87
Two-thirds (63 per cent.) gelatin N + one-third protein N	2	3620	51	14.53	13.82	+0.71
All protein N	2	3220	46	14.26	13.52	+0.74

Murlin[1] also showed that the sparing power of gelatin was due to its immediate chemical nature, and not to the 60 per cent. of glucose which can arise from it in metabolism (see p. 209). For example, to a fasting dog were given 12 grams of glucose daily for four days after thirteen days of fasting; then 20 grams of gelatin were substituted during a period of four days. The glucose scarcely exerted any sparing power over the protein metabolism, whereas the ingestion of gelatin showed the usual sparing of 31 per cent.

The same fact was demonstrated on a man who was brought into nitrogen equilibrium on an adequate mixed diet containing 10 grams of nitrogen and carbohydrates enough to supply 50 per cent. of the energy. The state of nitrogen equilibrium was not quite maintained when gelatin was used as the source of two-thirds of the nitrogen in the diet. Murlin explained this as being due to a dislike for sweets on the part of the individual so that he could not take carbohydrates in large excess. However, when the nitrogen of the diet was reduced so as to contain only protein nitrogen equal to one-third that eliminated in fasting, together with the 60 per cent. of glucose which could have originated from the gelatin previously ingested, the waste of body nitrogen rose far above that observed when gelatin and other protein were given. The experiment may thus be presented:

INFLUENCE OF GELATIN IN METABOLISM
(Figures are for the last day of each period)

Source of N in Diet	No. of Days	Cal. in Food	Cal. per Kg.	N in Food	N in Excreta	N to Body
				Grams	Grams	Grams
Meat + veg. protein N*	4	1971	43	10.05	10.35	−0.30
Two-thirds (67 per cent.) gelatin N + one-third veg. protein N	6	1935	42	9.62	10.12	−0.50
One-third veg. protein N	3	1858	40	3.23	5.62	−2.39

* Two-thirds meat N + one-third vegetable N in wheat, oats, and rice.

[1] Murlin, J. R.: Am. J. Physiol., 1907, **20**, 234.

Here the rise in the metabolism of body protein is coincident with the withdrawal of gelatin from the diet even in the presence of a considerable intake of carbohydrate. Hence Landergren's[1] interpretation that the rise in nitrogen elimination, which takes place on changing from a pure carbohydrate to a pure fat diet, is due to the body's absolute requirement for carbohydrate and that it obtains this by increasing its protein metabolism is scarcely tenable, although even now this point is emphasized by many writers.

It is evident that the "wear-and-tear" quota of protein metabolism must be covered by the ingestion of an equal "repair" quota, while the additional "dynamic" quota may be supplied by protein or by gelatin. Murlin found that the "repair" quota was best administered in the form of beef heart, and that the proteins of biscuit meal were very inefficient as sparers of body protein. These are among the earliest experiments of the kind.

Murlin also showed that three-quarters of the starvation nitrogen ingested as gelatin and one-quarter as meat protein were not able to maintain nitrogen equilibrium in the dog. Two-thirds the starvation nitrogen requirement ingested as gelatin and one-third as protein maintain nitrogenous equilibrium. Carbohydrates ingested alone reduce protein metabolism to one-third that found in starvation. One-third the starvation quantity seemed to be the lower limit of protein metabolism compatible with ordinary life. (See page 362.)

It may also be noted that in a fasting diabetic dog the protein metabolism may rise to fivefold that noted in simple fasting (see p. 634), or fifteenfold the *irreducible minimum* of the wear-and-tear quota. Under these circumstances the writer has found that pure gelatin given alone is more effective as a protein sparer than it is in simple fasting. Thus after giving 30 grams of gelatin to a fasting phlorhizinized dog the following results were obtained on analyzing the urine every twelve hours:

	Glucose, Gm.	N, Gm.	Body N, Gm.
Fasting, twelve hours	12.58	3.77	−3.77
Gelatin (= 4.644 g. N), twelve hours	20.66	6.02	−1.37
Fasting, twelve hours	.....	3.79	−3.79

If the fecal nitrogen, of which there is very little after gelatin ingestion, be neglected, it may be calculated that body protein was

[1] Landergren, E.: Inaugural Dissertation, Stockholm, 1902: Maly's Jahresbericht, 1902, p. 685.

spared after the administration of gelatin to the extent of 63.7 per cent. instead of 30 per cent. as in ordinary fasting. One may, therefore, conclude that the great waste of body protein which takes place in diabetes belongs in Rubner's category of dynamic protein metabolism, for which gelatin may be largely used as a substitute.

THE SYNTHESIS OF AMINO-ACIDS

Curiously enough, the endogenous protein metabolism appeared to be greatly reduced when ammonium acetate or nitrate was added to a rich carbohydrate diet. This subject was first studied by Grafe,[1] who announced that nitrogen equilibrium could be maintained with carbohydrate and ammonium acetate in the diet, and who saw in this a synthetic formation of protein within the organism. Even the ingestion of ammonium chlorid reduced the amount of protein metabolism. A paper by Abderhalden[2] followed quickly, which showed that though ammonium acetate when given with starch, sugar, fat, and bone-ash greatly reduced the endogenous metabolism, yet nitrogen equilibrium could not be attained under these circumstances. Abderhalden believes it possible that the animal cell may synthesize alanin, serin, or even cystein under these conditions, although he thinks that the heterocyclic and aromatic amino-acids are much less likely to be formed. He suggests that the mass action of ingested ammonia may prevent the deamination of some of the amino-acids, which may therefore be used once again for the repair of the tissue. Abderhalden's explanation seems the more rational of the two. A considerable sparing of endogenous protein metabolism was observed by Grafe[3] to take place after the administration of ammonium citrate with carbohydrate, and this has been confirmed by Underhill,[4] who, however, could find no influence exerted by ammonium chlorid.

More recently Gessler,[5] of Grafe's laboratory, states that, although after giving ammonium acetate and citrate to fasting dogs the negative balance of nitrogen is reduced, the sulphur balance remains exactly the same as before. The conclusion is drawn that ammonium salts are deposited in the body without affording any

[1] Grafe, E., and Schläpfer, V.: Z. physiol. Chem., 1912, **77**, 1.
[2] Abderhalden, E.: *Ibid.*, 1912, **78**, 1. A vast literature, experimental and polemical, has arisen from these two papers.
[3] Grafe, E.: Z. physiol. Chem., 1912, **82**, 347.
[4] Underhill, F. P., and Goldschmidt, S.: J. Biol. Chem., 1913, **15**, 341.
[5] Gessler, H.: Z. physiol. Chem., 1920, **109**, 280.

protection to the waste of body protein. The following is illustrative of the results obtained:

	Length of Period	Balance per Day		N:S
		N	S	
	Days	Gm.	Gm.	
Fore period	2	−1.78	−0.116	15.4
1.5 gm. N in NH_4-citrate daily	5	−1.22	−0.110	
After period	5	−1.66	−0.105	15.8

In conflict with this stands the statement of Caldwell and Clotworthy,[1] who find that ammonium acetate passes wholly into urea without retention of nitrogen, while ammonium chlorid is dissociated and passes in part to urea and in part to ammonia in the urine. These authors say, "Speculations concerning the synthetic powers of the body under conditions such as we have been investigating are very attractive, but we hesitate to make positive assertions." There the matter rests today excepting the proved power of the body to make glycin synthetically under the influence of benzoic acid ingestion.

Grafe[2] has announced that urea when given with carbohydrate protects body protein from waste just as ammonium citrate does. This is denied by Abderhalden.[3] Henriques and Andersen[4] explain Grafe's results as due to the growth of bacteria within the medium of the intestinal tract of herbivora. Rats may be maintained when given such bacterial masses as the source of their protein food.

Lower organisms have the power to synthesize protein from sugar and some simple source of nitrogen. Thus, Armand-Delille[5] found that the tubercle bacillus grew as well in a culture-medium of sugar, glycerol, glycin, and arginin, with addition of appropriate salts, as it did in a solution of 1 per cent. of peptone in bouillon.

Delbrück, in Germany, discovered that yeast cells developed rapidly and formed body protein when they were placed in a solution of sugar and ammonium sulphate. The mass thus developed is unpalatable.

[1] Caldwell, W., and Clotworthy, H. R. S.: Biochem. J., 1916, **10**, 14.
[2] Grafe, E., and Turban, K.: Z. physiol. Chem., 1913, **83**, 25.
[3] Abderhalden, E., and Lampé, A. E.: *Ibid.*, 1913, **84**, 218.
[4] Henriques, V., and Andersen, A. C.: *Ibid.*, 1914, **92**, 21.
[5] Armand-Delille, P., Mayer, A., Schaeffer, G., and Terroine, E. F.: Arch. de Physiol. et Path. gén., 1913, **15**, 797.

Lower organisms may therefore form the various aliphatic, aromatic, and heterocyclic amino-acids from carbohydrate and ammonium salts.

Within the body of the mammal it is possible that some of the simpler deamination reactions are reversible (see pp. 219, 234), but the experiments with gelatin demonstrate that when tryptophan and cystin are lacking these important building-stones of protein cannot be synthesized, for nitrogen equilibrium can be obtained only when they are mixed with the gelatin food. The consideration of other "deficient" proteins will be given elsewhere (see p. 511).

The cause of the great reduction in the fasting quantity of protein metabolism when carbohydrates alone are ingested has been thus stated by Knoop:[1] "The animal body may therefore synthesize amino-acids from ammonia. If amino-acids can be produced from oxyacids, such as originate from carbohydrate metabolism, for example, then it is possible to comprehend chemically not only the production of sugar from protein but also reactions in a reverse direction. The minimal nitrogen metabolism of fasting may be reduced either through the ingestion or through the intermediary production of non-nitrogenous acids, which unite with ammonia prior to its synthesis to urea and form amino-acids."

Since amino-acids when ingested tend to reduce protein metabolism this seems a plausible hypothesis. However, one should bear in mind the experiment of McCollum (see p. 225), in which 37 per cent. of the urinary endogenous protein nitrogen could be removed in the form of glycin when benzoate of soda was ingested without affecting the amount of protein metabolism. This glycin nitrogen when once bound as hippuric acid could not have participated in any interplay of chemical reaction with keto- or oxyacids produced in carbohydrate metabolism.

Rubner has called attention to the extremely soluble character of the monosaccharids, and it may be that a plethora of carbohydrate molecules reduces the demands upon the structural protein of the cells. Furthermore, it has been noted that the production of β-oxybutyric acid is associated with an increased protein breakdown (see p. 95), so that the action of carbohydrate may perhaps prevent chemical injury to the cellular framework by promoting the normal oxidation of β-oxybutyric acid.

[1] Knoop, F.: Z. physiol. Chem., 1910, **67**, 489.

It has been reported by Kostytschew and Brilliant[1] that a chemical union takes place between amino-acids and carbohydrates in solution. Von Euler[2] and his school picture the union of the aldose group of glucose with glycin as follows:

$$R—CHOH—CH:N—CH_2COOH$$

In dilute solutions 22 per cent. of the glycin may thus unite with glucose with depression of the optical rotation. d-l-Alanin also combines with glucose. Neuberg and Kobel[3] announce that if the carbohydrates, glucose, fructose, maltose, or hexose-phosphoric acid, be mixed with l-alanin, asparagin, glutamic acid, or arginin, there are changes in the optical rotation of the solution and changes in the readiness of fermentation.

Working in the Cornell laboratory, Chambers and Milhorat have been led to suspect that the slight increases in nitrogen elimination during the early periods of muscular exercise in a fasting dog were due to the liberation of amino-acid complexes united with glycogen (see pp. 405, 642).

Whether this chemical union of glucose with amino-acids is strong enough to prevent deamination by the liver and to allow the amino-acids to pass untouched to the tissues for renewed utilization, is of course unknown, but such a course suggests a possible explanation of the protecting power of carbohydrate over protein metabolism.

CARBOHYDRATES AND PROTEIN RETENTION

Since carbohydrates so effectively spare protein from combustion, it would seem logical that their use should render the retention of protein in the body easier than when fat is given with protein.

Lüthje[4] finds a long-continued nitrogen retention in man when much nitrogen in protein is ingested (up to 50 gm. N daily!) and carbohydrates and fat making a total of 4000 calories or 66 calories per kilo. (See also Bornstein's experiment, p. 188.)

In a subsequent paper Lüthje[5] finds that the P_2O_5 retention in convalescence is that which corresponds to the retention of protein for the formation of new tissue, including bone. Sometimes in a

[1] Kostytschew, S., and Brilliant, W.: Z. physiol. Chem., 1923, **127**, 224.
[2] von Euler, H. (with K. Josephson and E. Brunius): *Ibid.*, 1926, **153**, 1; **155**, 259; **161**, 265.
[3] Neuberg, C., and Kobel, M.: Biochem. Z., 1926, **174**, 464.
[4] Lüthje, H.: Z. klin. Med., 1902, **44**, 22.
[5] Lüthje, H., and Berger, C.: Deut. Arch. klin. Med., 1904, **81**, 278.

healthy person not enough P_2O_5 is retained to build up "flesh," and the protein retained must, therefore, exist in the form of "deposit protein." This protein, he says, is not stored in the blood, for the composition of the blood does not alter, but is perhaps retained in the cellular fluids, just as glycogen is retained by the cells.

Rubner states that the greater the impoverishment of the protein supply in an animal fed with fat, the more powerful is the protective effect of small quantities of ingested protein over the loss of body protein. Also the retention of protein depends on the protein content of the animal as well as on the quantity of protein ingested. This is illustrated in the following table:

INFLUENCE OF THE PROTEIN CONTENT OF A DOG ON THE RETENTION OF PROTEIN INGESTED

Total N Content of Dog, Gm.	N in Terms of 100 N in Dog in Food	to Body
318.8	5.25	+1.65
354.7	5.57	+1.02
310.6	6.72	+2.64
363.7	12.79	+2.62

It is evident from this that of the same diet of protein more will be retained when the nitrogen content of the dog is low than when it is high; and also that a small protein intake may cause the same retention of nitrogen as a large protein intake, if in the first instance there be a relative impoverishment of the protein content of the animal.

According to these laws adult cells which have been depleted of their protein may gradually improve their nutritive condition until they reach an *optimum*, at which point they lose their power to attach additional protein.

This is also illustrated in an experiment by McCollum,[1] who gave to a hog a diet containing 14 grams of nitrogen per day in the form of casein and starch, so that the value of the diet was 100 calories per kilogram during a period of thirty-six days. The animal retained 43 per cent. of the nitrogen ingested. During the first three days it added 9.65 grams of nitrogen to the body daily; during the last three, 3.69 grams. With the increase in active protoplasm the creatinin nitrogen excretion rose from 0.24 to 0.31 gram per day.

Csonka[2] gave to a young hog, nourished with starch, the wear and tear urinary nitrogen of which was 0.87 gm. or 56 mg. per kilogram of body weight, casein containing 6.16 gm. nitrogen daily, or 18.5 gm.

[1] McCollum, E. V.: Am. J. Physiol., 1911–12, **29**, 215.
[2] Csonka, F. A.: J. Biol. Chem., 1924, **60**, 545.

during a period of 3 days. The urine of the 3 days contained only 6.4 gm. Nearly two-thirds of the casein ingested must have been deposited by the rapidly growing animal.

Rubner[1] gave to five people who were greatly emaciated by the war diet of blockaded Germany—they had lost 30 per cent. in weight—diets containing both high and low amounts of protein but with adequate caloric content for periods of 5 days and witnessed the following additions of protein nitrogen to their bodies:

Cals. in Diet per Day	N in Diet per Day, Gm.	N to Body per Day, Gm.
2390	4.15	±0
2072	5.05	+ 0.5
1932	10.8	+ 3.8
3497	14.5	+ 5.7
1757	15.1	+ 6.4
1862	15.5	+ 7.6
3088	20.0	+ 8.8
2124	20.2	+10.2
3146	29.3	+17.2

In these experiments the deposit of protein was never complete. In the last experiment, for example, assuming 4.1 gm. of protein nitrogen to be the minimum level of nitrogen equilibrium, Rubner writes the following balance sheet:

Daily diet contained	29.3 gm. N
Less N minimum (repair quota)	4.1
Available for deposit	25.2
Actually deposited	17.2 = 68 per cent.

The average for the series shows that, of the excess above, the minimum—*i. e.*, of the amount available for deposit—about 60 per cent. (maximum 68 per cent.; minimum 54 per cent.) was retained in the body.

Rubner calculates, if a well-nourished man with an original nitrogen content in protein of 2100 gm. be given a diet adequate in calories but so low in protein that he loses at first 1 gm. nitrogen per day, that he will come into nitrogen equilibrium after 1050 days, having lost an average of 0.5 gm. nitrogen per day or 525 gm. of body nitrogen during a period of 3 years. This would be one-quarter of his total stock of protein.

In reconditioning this man, if he took 6.8 gm. of nitrogen daily it would require 471 days, or a year and a quarter, to restore the lost body protein. If, however, he took 28.6 gm. of protein nitrogen

[1] Rubner, M.: Arch. f. Physiol., 1919, p. 24.

daily, the restitution of the lost protein would require only 38 days. In the first case 16 per cent. of the total protein nitrogen ingested would be deposited; in the second 48 per cent.

Rubner states that these are purely theoretical calculations.

The conditions of protein metabolism are entirely similar to those of starch metabolism: (1) Digestive hydrolysis; (2) partial combustion of the end-products; and (3) possible regeneration of portions of the end-products into substances akin to the originals but characteristic of the organism—*i. e.*, glycogen and body proteins. In the case of proteins the second or metabolic process involves the production of sugar and of fatty acids from the amino-acids involved. The third or regenerative process is promoted by such a protein as casein, which yields the proper variety of cleavage products.

In conclusion, it may be said that carbohydrates are the most economical of the food-stuffs, both physiologically and financially. They are the greatest sparers of protein. Ingestion of fat has for its object the relieving of the intestine from excessive carbohydrate digestion and absorption. Ingestion of fat in too large quantities leads to digestive disturbances, and if carbohydrates are entirely abandoned, to acetonuria.

CHAPTER XVI

THE INFLUENCE OF THE INGESTION OF CARBOHYDRATE
(Concluded)

PART III—THE RESPIRATORY METABOLISM

The proper nutrition of man concerns no one, not even those classes which should take the subject most to heart, and it is rare to find anyone who has a proper understanding of the subject. This short-sighted attitude is because such knowledge cannot be expressed in terms of money. It is analogous to the short-sightedness of the peasant who gives more attention to the nutrition of his cattle, whose meat and milk he sells, than he does to that of his children.—Carl Voit (in 1876).

In a previous chapter (see p. 282) it has been stated that when Rubner gave cane-sugar to a dog and measured the metabolism during a period of twenty-four hours, the heat production was raised by an increment amounting to about 6 per cent. of the calories ingested. This fact, which has been repeatedly confirmed, does not tell the whole story, because the absorption of the very soluble sugar takes place in the first few hours. Thus Magnus-Levy[1] noticed that after giving 155 grams of cane-sugar to a man there was a maximal increase in metabolism of 12 per cent., with a return to the basal level during the fifth hour after taking the food-stuff.

Johansson, Billström, and Heijl[2] have shown that if 50 to 200 grams of cane-sugar be given to a fasting man, the carbon dioxid output increases from 22.6 grams per hour to about 30 grams per hour. The larger ingestion did not produce a higher elimination of carbon dioxid than does the smaller amount. This indicates the evenness with which sugar entering the blood-stream is utilized by the organism. If sugar be present in excess it may be stored as glycogen until it is needed by the cells. The rise in the carbon dioxid output is greater after fructose is ingested than after glucose is given. This was explained as due to the fact that fructose is less readily retained in the liver as glycogen, and therefore reaches the tissues in a larger stream than does glucose under similar circumstances, and hence more completely replaces fat as the source of energy. In a later paper

[1] Magnus-Levy, A.: Pflüger's Arch. gesam. Physiol., 1894, **55**, 1.
[2] Johansson, J. E., Billström J., and Heijl, C.: Skan. Arch. Physiol., 1904, **16**, 263.

Johansson[1] explains that after ingesting 200 grams of glucose containing 740 calories, or one-quarter the man's energy requirement for a day, the rise in carbon dioxid output lasts for six hours and then falls to the fasting basis. This is an indication of the ready absorption and combustion of ingested glucose. If there has been prolonged fasting, this author states that ingested glucose may cause no rise in the carbon dioxid output in man on account of its conversion into glycogen. (See page 356.)

Durig[2] gave 100 grams of glucose to a man and compared the metabolism with that obtained after giving 100 grams of fructose. In the latter case the heat production as measured by indirect calorimetry was 10 per cent. greater than in the former; the respiratory quotients were usually higher, being more frequently over unity, and therefore indicating a readier conversion of fructose into fat than was the case with glucose.

Du Bois[3] made calorimetric observations on men after giving 100 and 200 grams of glucose and noted the following increases above the basal metabolism:

PERCENTAGE INCREASE IN HEAT PRODUCTION AFTER GIVING GLUCOSE TO MAN

Hours after Food	1	2	3	4	5
Subject E. F. D. B., 100 grams glucose	3	11	9	6	
(*R. Q.*)	(0.91)	(0.89)	(0.88)	(0.90)	
Subject E. F. D. B., 200 grams glucose	..	13	17	8	7
(*R. Q.*)	..	(0.95)	(0.93)	(0.95)	(1.00)
Subject L. C. M., 200 grams glucose	..	24	16	16	
(*R. Q.*)	..	(0.92)	(1.00)	(1.02)	

One hundred grams of glucose caused an average increase of 9 per cent. in the heat production and 200 grams one of 12.5 per cent. during three to six hours after their ingestion by a man of 75 kilograms in weight. Ingestion of 200 grams of glucose by a man of 60 kilograms weight caused an increase of 16 per cent. in the heat production. When the larger quantity was administered, the respiratory quotients indicated that the heat production was entirely at the expense of carbohydrate and protein.

[1] Johansson, J. E.: Skan. Arch. Physiol., 1909, **21**, 30.
[2] Tögel, O., Brezina, E., and Durig, A.: Biochem. Z., 1913, **50**, 298.
[3] Gephart, F. C., and DuBois, E. F.: Arch. Int. Med., 1915, **15**, 835.

BLOOD SUGAR IN MAN

It is interesting to observe that as a rule the period of high metabolism after glucose ingestion coincides with an increased quantity of glucose in the blood stream. The following results were obtained after giving glucose to men:

Subjects	Amount of Glucose	Blood Sugar in Per Cent.				
		Basal 8 A. M.	½ Hour	1 Hour	2 Hours	3 Hours
	Gm.					
Average 8 normal persons[1]	100	0.076	0.108	0.093	0.083	0.078
Mr. M.[1]	150	0.10	0.122	0.125	0.105	0.10
Mr. M.[1]	200	0.11	0.143	0.154	0.119	0.10
Average normal[2]	100	0.09	0.14	0.12	0.11	0.09
Maximum[1]	100	0.16	0.23	0.28	0.26	0.17

Bock, Schneider, and Gilbert[3] state that after giving 110 gm. of glucose to a man the initial rise of blood sugar may take place in three minutes, may rise from a basal level of 0.11 per cent. to 0.245 per cent. in 30 minutes, and become nearly normal again (0.12 per cent.) in 1 hour and 20 minutes.

Hansen[4] finds that after giving 50, 100, 200, and even 400 gm. of glucose to man the blood sugar rises from a basal level of 0.09 per cent. to one which does not usually exceed 0.18 per cent. Oxidation, glycogen formation, or conversion into fat cares for the excess of sugar molecules entering the blood stream.

The removal by the body tissues of the excess of glucose present in arterial blood after giving 75 gm. of glucose is shown in the following table given by Turban[5]:

INFLUENCE OF GLUCOSE ABSORPTION ON THE BLOOD SUGAR, IN PER CENT.

	9 A. M. Post-absorptive		10:46 A. M.		11:15 A. M.		12:15 P. M.		2:30 P. M.		6:30 P. M.	
	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.
75 gm. glucose *per os* at 10:30 A. M.	0.099	0.094	0.126	0.124	0.165	0.158	0.197	0.169	0.140	0.120	0.098	0.091

[1] Strouse, S.: Arch. Int. Med., 1920, **26**, 759.
[2] Gray, H.: *Ibid.*, 1923, **31**, 241.
[3] Bock, J. C., Schneider, H., and Gilbert, M.: J. Biol. Chem., 1926, **69**, 9.
[4] Hansen, K. M.: "Investigations on the Blood Sugar in Man," Copenhagen, 1923.
[5] Turban, K.: Z. physiol. Chem., 1922, **119**, 4.

Similar results were obtained by Henriques and Ege,[1] who also stated that, following a heavy glycogen charge of the muscles, venous blood might become richer in glucose than arterial blood.

Folin and Berglund[2] point out that fructose and galactose are far less efficient in raising the level of the blood sugar than is glucose. As to galactose, it is very readily eliminated in the urine. Rowe,[3] in a carefully executed piece of work, states that the *tolerance* for galactose is 30 gm. in a man and 40 gm. in a woman; that is to say, these amounts are necessary to provoke its elimination in the urine. That the tolerance is dependent on sex is explained by the fact that woman in her adult years has a specific galactose mechanism inherent in the mammary glands which, so far as is known, is lacking in man. As regards fructose, its behavior may be due to its readier oxidation, the cause of which may possibly lie in its dihydroxyaceton radicle. For not only is fructose oxidized with great quickness in the body, but dihydroxyaceton is also. This was beautifully shown by Mason,[4] who compared the influence of glucose, 25 gm., and dihydroxyaceton, 25 gm., upon the metabolism of man. The results were as follows:

THE RESPIRATORY AND CARBOHYDRATE METABOLISM OF DIHYDROXYACETON IN NORMAL MEN

	Glucose, 25 Gm.			Dihydroxyaceton, 25 Gm.		
	R. Q.	Blood Sugar Per Cent.	Cals. per Hour	R. Q.	Blood Sugar Per Cent.	Cals. per Hour
Basal	0.82	0.14	54.2	0.77	0.11	53.1
30 min.	0.75	0.15	55.4	1.00	0.09	61.4
60 min.	0.82	0.13	59.8	0.89	0.08	60.4
2 hrs.	0.82	0.11	56.7	0.82	0.09	53.7
3 hrs.	0.74	0.10	55.5	0.71	0.10	51.5

The immediate rise both of the metabolism and of the respiratory quotient during the first hour after giving dihydroxyaceton to man, without any increase in the amount of blood sugar, can easily be interpreted to mean that it is swiftly and directly utilized without the necessity of passing into the form of a sugar. This accords with what is known of its behavior in hypoglycemic shock (p. 340).

[1] Henriques, V., and Ege, R.: Biochem. Z., 1921, **119**, 121.
[2] Folin, O., and Berglund, H.: J. Biol. Chem., 1922, **51**, 213.
[3] Rowe, A. W.: Arch. Int. Med., 1924, **34**, 388.
[4] Mason, E. H.: J. Clin. Invest., 1925–26, **2**, 521.

THE BEHAVIOR OF CARBOHYDRATE IN DOGS

Extensive calorimetric observations upon dogs have been carried out in the author's laboratory, and the following principles are believed to have been established:

After giving 50 grams of glucose to a dog Fisher and Wishart[1] found an increase in the percentage quantity of blood-sugar at the end of the first hour, and this was followed by a fall to the normal level. A similar phenomenon had been observed in man[2] after giving 150 grams of glucose; but in the dog it was further observed that when the sugar solution was given there was at first a considerable reduction in the quantity of urine eliminated. This appears from the following analysis:

QUANTITY OF URINE AS INFLUENCED BY FASTING AND BY WATER AND GLUCOSE INGESTION

Hour	Fasting	150 C.C. Water	Glucose 50 Gm. in 150 C.C. Water	Glucose 75 Gm. in 150 C.C. Water
	C.C.	C.C.	C.C.	C.C.
1	7	28	7	6
2	2	27	7	6
3	4	28	12	7
4	3	17	100	19
5	..	..	66	89
6	..	..	22	

These authors also found that the hour of the sudden increase in the quantity of urine eliminated coincided with the completion of the absorption of glucose from the gut, and with the last hour of increased metabolism as determined in Lusk's calorimeter experiments. These circumstances led them to investigate the hemoglobin content of the dog's blood. They discovered that although at the end of the first hour there was no alteration in this regard, yet at the end of the second hour, when between two-thirds and three-quarters of the ingested sugar had been absorbed from the intestine, the blood usually became more dilute, as shown by a fall in the percentage amount of hemoglobin. This indicates the continuance of a generous distribution of glucose molecules to the tissues by means of an increase in the volume of the nourishing fluid.

With the cessation of absorption and the return of the blood to its normal volume the metabolism falls to its basal level, the respira-

[1] Fisher, G., and Wishart, M. B.: J. Biol. Chem., 1912–13, **13**, 49.
[2] Gilbert, A., and Baudouin, B.: Compt. rend. soc. biol., 1908, **65**, 710.

tory quotient frequently falls, and there is every indication of a regulation of the carbohydrate supply to the tissues by the liver so that fat and carbohydrate are oxidized together. Only when this food supply is supplemented by carbohydrate from the gut does the metabolism rise. Such an increase may, therefore, be properly termed the "metabolism of plethora." It was furthermore shown that during the period of absorption there was little retention of

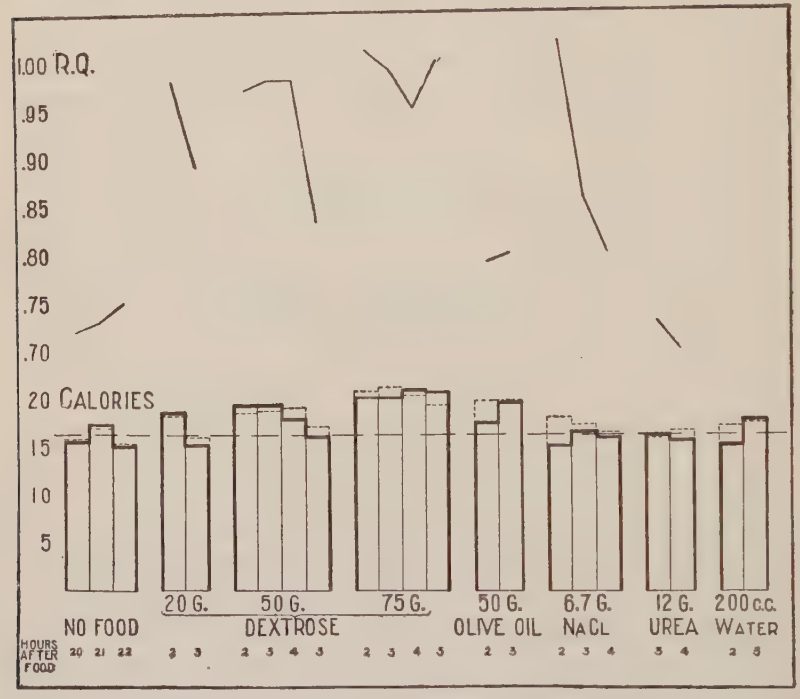


Fig. 24.—Illustrating the effect of the ingestion of glucose and fat and of water, urea, and salt solutions on the metabolism. Solid lines—metabolism in calories as calculated (indirect calorimetry). Broken lines—metabolism in calories as found (direct calorimetry).

glycogen by the liver—the absorbed glucose apparently passed freely into the tissues. The largest glycogen content of the liver was found during the last hour of absorption, the last of high metabolism, and the hour characterized by passage of a large volume of urinary water. This was the hour when the liver assumed the duty of arbiter over the carbohydrate supply to the cells. This work has been confirmed by Gigon.[1]

[1] Gigon, A.: Z. klin. Med., 1924, **101**, 17.

The calorimetric and respiratory experiments which established these interrelations are portrayed in the accompanying chart (Fig. 24).

The experiments showed that the height of the metabolism was about the same whether 50 or 75 grams of glucose were given, only in the latter case the effect was more prolonged. This is in accord with Rubner's idea of "self-regulation," and also accords with the fact that the fermentative activity of living yeast cells is independent of the concentration of the sugar solution in which they live.[1]

THE CAUSE OF THE SPECIFIC DYNAMIC ACTION OF CARBOHYDRATE

What is the cause of the increased metabolism after the ingestion of glucose? In Fig. 24 it appears that the administration of 150 c.c. of water, either alone or containing 6.7 grams of sodium chlorid or 17 grams of urea, has no effect upon the heat production. Therefore neither osmotic exchanges nor increased kidney function, nor intestinal absorption can play any part in the increased heat production.

These experiments led to further investigations[2] to inquire into the cause of the rise in heat production after glucose ingestion. To this end various carbohydrates were given to the same dog in quantities of 50 grams. The fact that fructose exerted a more powerful influence on metabolism than glucose was confirmed. It was also shown that galactose oxidized with much greater difficulty in the dog than the other two monosaccharids, as evidenced by a lower metabolism and a lower respiratory quotient, and that lactose was not oxidized at all, and therefore caused no increase in the heat production. This latter fact must have been due to the absence of lactase from the intestine. These relations are shown in the following table:

INFLUENCE OF 50 GRAMS OF VARIOUS CARBOHYDRATES UPON THE METABOLISM OF THE DOG

Experiment No.	Sugar 50 Gm.	Average R. Q.	2, 3, and 4 Hours: Percentage of Increase over Indirect Basal Metabolism
34, 36	Glucose	1.00	30
64, 66, 67	Fructose	1.02	37
60, 58	Sucrose	1.02	34
67	Galactose	0.93	22
62	Lactose	0.90	3

[1] Rubner, M.: Sitzungsber. k. preuss. Akad. Wissensch., 1913, **8**, 232.
[2] Lusk, G.: J Biol. Chem , 1915, **20**, 555.

Weinland[1] has shown that galactose does not form glycogen as readily as do glucose and fructose. From these facts it is most probable that galactose does not so readily dissociate into easily oxidizable molecules as do glucose and fructose. By similar reasoning one may explain the difference in behavior between glucose and fructose. Glucose molecules require simple dehydration for conversion into glycogen and may in that fashion be removed from the tissue fluids. Fructose cannot be thus removed. It must first undergo chemical change, and perhaps fragmentation into dihydroxyaceton with its three-carbon chain (formula on p. 348) before it can be synthesized into glycogen. These molecules being then in greater mass than similar molecules derived from ingested glucose would have been, it is easy to conceive that a higher metabolism would result on account of the greater plethora of oxidizable particles. F. G. Benedict[2] states that the cause of the specific dynamic action of carbohydrates is the formation of acids, which act as stimuli. In support of this he cites an experiment by Benedict and Joslin,[3] in which an increase of 30 per cent. in the heat production of a diabetic woman took place after the ingestion of 100 grams of fructose, notwithstanding the fact that the respiratory quotient before and after administration of the sugar was 0.69, indicating that none of the fructose was oxidized. Since fructose is transformed into glucose in the diabetic organism, Benedict interpreted this experiment as indicating the formation of acid intermediary products which stimulated metabolism.

Lusk has proved that when 12.5 grams of glycin, which are convertible into 10 grams of glucose, are given to a phlorhizinized dog, the heat production is largely increased (see p. 296). Not so, however, with fructose. When 10 grams of fructose, which are convertible into 10 grams of glucose, are given to a phlorhizinized dog there is no increase whatever in metabolism. The chemical intermediates between fructose and glucose are without stimulating influence. This appears in the following experiment:

[1] Weinland, E.: Z. f. Biol., 1899, **38**, 16, 607.
[2] Benedict, F. G.: Trans. XVth Internat. Congress of Hyg., 1912, **2**, 394.
[3] Benedict, F. G., and Joslin, E. P.: "Metabolism in Severe Diabetes," Carnegie Institution of Washington, Pub. 176, 1912, p. 69.

THE INFLUENCE OF FRUCTOSE IN PHLORHIZIN GLYCOSURIA

Exp. No.	Conditions	Hours	Urinary D:N	R. Q.	Non-protein R. Q.	Calories	
						Protein	Total Indirect
81	Eighth day fasting and phlorhizin	1	4.22	0.719	0.75	7.04	26.57
		2	4.22	0.711	0.74	7.04	27.62
	Average	..	....	0.715	....	....	27.10
	Same after fructose 10 gm	2	7.31	0.697	0.72	6.08	25.80
		3	7.31	0.697	0.72	6.08	25.80
		4	7.31	0.680	0.70	6.08	24.78
	Average	..	....	0.692	....	....	25.46

The fact that the ingestion by a phlorhizinized dog of alanin, which certainly yields lactic or pyruvic acids in metabolism, causes a considerable rise in the heat production, (see p. 304), led to the belief that such acids are not intermediary metabolites in the reaction which converts fructose into glucose.

This question cannot be regarded as entirely settled. In the tabular presentation of the experiment of E. H. Mason cited on p. 378 there is a record of specific dynamic effect following the ingestion of 25 grams of glucose by a man, although in this experiment there was no increase in the respiratory quotient above that of the basal metabolism previously ascertained. Similar results have been observed by Deuel[1] and by Cathcart and Markowitz.[2] Unpublished work from our laboratory and from that of the Russell Sage Institute of Pathology leads to the consideration of the possibility that there may be an intermediary fragmentation of both glucose, as well as of fructose, before they are converted into glycogen, and that energy liberation and absorption may be needed in the process. This would, in part at least, explain the specific dynamic action of carbohydrate.

Benedict[3] goes so far as to intimate that the long neglected experiments of Grouven (1864), purporting to show that in the steer carbohydrate is not absorbed as glucose but is all converted into fatty acid in the intestine, are evidence that following carbohydrate ingestion fatty acids pour into the blood and stimulate to a high metabolism in these animals. If glucose were converted into fatty

[1] Deuel, H. J., Jr.: J. Biol. Chem., 1927, **75**, 367.
[2] Cathcart, E. P., and Markowitz, J.: J. Physiol., 1927, **63**, 309.
[3] Benedict, F. G., and Ritzman, E. G.: Proc. Nat. Acad. Sc., 1927, **13**, 125.

acid in the intestine it would never be possible to recover it in the urine of the diabetic animal.

It may be added that if much acid be produced in carbohydrate metabolism, one would expect to find an increased quantity of ammonia in the urine during the oxidation of carbohydrate, just as ammonia elimination increases when lactic acid is formed in phosphorus poisoning, but such an increase is not observed.[1] Furthermore, if there were a considerable production of acid as a result of carbohydrate oxidation one would expect to find a fall in the quantity of carbon dioxid in the blood, such as occurs after giving meat, whereas unpublished experiments done by Dr. A. L. Meyer in the author's laboratory show that this is not the case—the quantity of carbon dioxid remains unchanged (see p. 299).

It is interesting to note that Freise[2] found that when a surviving dog's liver is perfused with blood it yields 55 to 192 milligrams of carbon dioxid per minute per kilogram of substance. Addition of glucose, pyruvic acid, lactic acid, or glyceric acid increases the carbon dioxid 50 per cent., whereas galactose, glyoxylic, glycollic, and acetic acids were without influence.

It is, of course, known that the end-product of sugar metabolism, carbonic acid, is a stimulus to the respiratory center, but the end-product cannot be the cause of its own increased production for the following reasons:

When the supply of carbohydrate exceeds the capacity of the organism to store it as glycogen or to oxidize it, then its metabolites are converted into fat with the elimination of carbon dioxid. The greater the amount of fat thus formed, the greater the carbon dioxid elimination. But since very different quantities of fat may be formed at the same level of total metabolism, it appears that neither the extra production of carbon dioxid nor the production or deposit of fat has to do with the level of the total metabolism. These points are illustrated in the experiments on the dog (p. 397) and on the hog (p. 399) which portray the conversion of carbohydrate into fat.

Woodyatt,[3] using a pump of his own invention, finds that he can administer continuous intravenous injections of glucose solutions at the rate of 1 gm. of glucose per hour per kilogram of body weight to a dog weighing 10 kg., 18 hours after food, without more than 0.3 gm.

[1] Murlin, J. R., and Lusk, G.: J. Biol. Chem., 1915, **22**, 15.
[2] Freise, E.: Biochem. Z., 1913, **54**, 474.
[3] Felsher, H. V., and Woodyatt, R. T.: J. Biol. Chem., 1924, **60**, 737.

of urinary sugar appearing in 4 hours, but on raising the quantity injected to 1.1 gm. per kg. and hour, 5.8 gm. appeared in the urine of the same period. Boyd, Hines, and Leese[1] have combined this method with respiration experiments. They injected 4 gm. of glucose per kg. body weight per hour. The blood sugar rose rapidly from 0.1 per cent. to 0.7 per cent. and remained constantly at that level. One hour after completion of the injection the blood sugar had returned to the normal level. Their results are thus written:

	Cals. per Sq. Meter per Hr.
Basal metabolism	43.3
Injection of glucose	63.9*
1 hr. after	50.4
2 hrs. after	48.5
3 hrs. after	45.5

* The increase over the basal is 48 per cent.

Here, with 0.7 per cent. of glucose in the blood under quite artificial conditions, the maximal increase in metabolism ever recorded in a dog after glucose administration was obtained. The dog's tissues, however, cannot oxidize glucose by doubling the metabolism as do those of the hog. Is the hog prone to "constitutional" obesity?

It would seem that the chief cause of the increased heat production after carbohydrate ingestion lay in the plethora of metabolites, which the cells, within the limits of the definite upper level imposed by self-regulation, were capable of utilizing. Above this level the metabolites are convertible into fat with little loss in the original energy content of the sugar from which they arise.

THE SUMMATION EFFECT OF COMBINATIONS OF AMINO-ACIDS, CARBOHYDRATES AND FATS

The subject may be approached from still another standpoint, combining the influence of carbohydrate with that of amino-acids and other food-stuffs. The following observations have been made by the author.[2] When 50 grams of glucose were administered to a dog the heat production increased 30 per cent.; with 70 grams, the increase was 35 per cent. Twenty grams of glycin increased it 36 per cent., and the same amount of alanin, 32 per cent. Combined,

[1] Boyd, J. D., Hines, H. M., and Leese, C. E.: Am. J. Physiol., 1925, **74**, 656.
[2] Lusk, G.: Jour. Biol. Chem., 1915, **20**, 555.

50 grams of glucose and 20 grams of glycin are the glucose equivalent of 66 grams, and yet when they were given together the metabolism increased 56 per cent., an increase greater than 66 grams of glucose could have induced. Glucose and alanin in similar quantities are a glucose equivalent of 70 grams and caused an increase in heat production of 53 per cent. It is obvious that an increase in the quantity of glucose when this is given in large amounts scarcely affects metabolism; but that the chemical stimulus of amino-acids acting in conjunction with a plentiful supply of glucose results in a rise in heat production which is nearly the sum of the two individual influences acting separately. This points to a distinct difference between the cause of the specific dynamic action of glucose and that of alanin, which latter is convertible into lactic or pyruvic acid and eventually into glucose.

The metabolites of alanin or glycin may therefore raise the level of cell activity; and if fragments of glucose metabolism be present in quantity, these may enter as increased fuel to produce yet higher metabolism in the cells than the oxyacids would alone induce.

Also, Lusk showed that when alcohol is given with glucose the metabolism rises above the level it would have attained had glucose been administered alone. The respiratory quotient falls, the cells oxidize both alcohol and the fragments of glucose metabolism, and produce almost as much extra heat as the sum of the quantities of heat which each material would have induced alone.

The effect of alcohol in depressing the respiratory quotient in man is well shown by Brechmann[1] in the following table:

Time	Alcohol 30 Gm. at 2.45 P. M. R. Q.	No Alcohol R. Q.
12.00 Basal	0.93	0.99
1.00 Fructose, 60 gm.		
2.15	1.04	1.00
3.15	0.86	1.04
3.25 Fructose, 40 gm.		
4.00	0.88	1.01
5.30	0.89	1.04

The experiments of Lusk were extended by Murlin and Lusk,[2] so that the influence of glycin, glucose, and fat when ingested severally and together could be analyzed.

[1] Brechmann, H. J.: Z. f. Biol., 1925, **83**, 325.
[2] Murlin, J. R., and Lusk, G.: J. Biol. Chem., 1915, **22**, 15.

It was found that if glucose be ingested at the time of the highest fat metabolism, the heat production undergoes a second increase to the same extent to which glucose alone would have increased metabolism. At this level of higher metabolism the respiratory quotient is 0.93 or 0.94, instead of unity, which it would have been if glucose had been given alone, hence glucose and fat are being oxidized together. The urinary ammonia fell following the ingestion of glucose four hours after fat ingestion, and this was true in spite of the combined oxidation of fat and carbohydrate. This does not suggest the occurrence of acid formation as the cause of the high metabolism.

When glucose and glycin (glycocoll) are given together so that their molecules enter the circulation at the time of the height of fat absorption, the increase in metabolism is very nearly equal to the sum of the increases which each of the three materials would have induced alone.

The following table and accompanying chart (Fig. 25, p. 388) show these relations:

THE EFFECT OF GLYCIN, GLUCOSE, AND FAT, SEVERALLY AND TOGETHER

(Dog XIV. Second series)

Experiment Nos.		R. Q.	Cal. per Hour	No. of Hours	Increase Over Normal	
					Cal.	Pr. Ct.
15, 17, 21	Basal	0.86	22.7	3		
20	Fat, 75 grams	0.80	26.6	4*	3.9	17
18	Glycin, 20 grams	0.90	27.6	2	4.9	25
16, 19	Glucose, 70 grams	1.02	29.6	2	6.9	30
23	Glucose, 50 grams + glycin, 20 grams	1.03	33.5	2	10.8	48
24	Glucose, 50 grams + glycin, 20 grams, given four hours after fat, 75 grams	1.02	37.3	2	14.6	64

* Hours 6, 7, 8, 9 after fat ingestion.

From the data obtained with this dog the following computation may be made, which shows that the sum of the individual increases of heat production caused by each substance is only a little more than the total heat production when all the substances are given together:

	Calories	Per Cent.
Glycin, 20 grams	4.9	25
Glucose, 70 grams	6.9	30
Fat, 75 grams	3.9	17
Sum of all	15.7	72
Glycin, 20 gm., + glucose, 50 gm., 4 hrs. after fat, 75 gm.	14.6	64

It would seem that the old idea of "*luxus consumption*," recently regarded as proved by Grafe, could be explained on the basis of the forgoing analysis of the summation effect of the specific dynamic

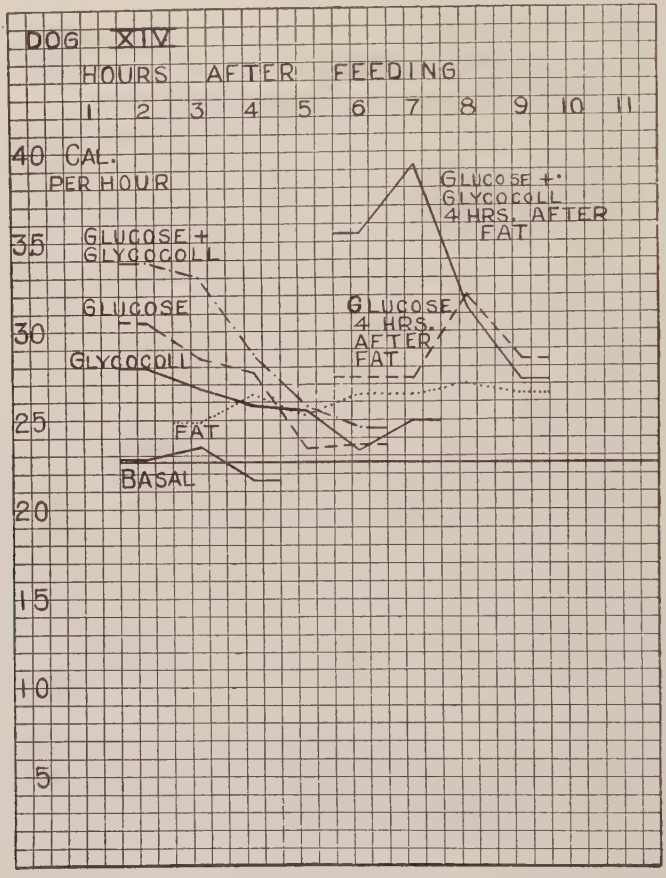


Fig. 25.—The effect of fat, of glycin, of glucose, of glucose + glycin, and of glucose + glycin + fat upon the heat production. (The "glucose four hours after fat" curve is atypical, is not similar to other experiments, and probably denotes a slow emptying of the stomach.)

action of the various food factors. According to Grafe "luxus consumption" is the adaptation of the body to an increased metabolism after a large influx of food. Eckstein and Grafe[1] have given to a

[1] Eckstein, E., and Grafe, E.: Z. physiol. Chem., 1919, **107**, 73

dog, the basal metabolism of which they compute as being 50 calories per kilogram of body weight per day, daily for 14 days a diet containing 202 calories per kilogram of body weight and containing 10.74 gm. protein nitrogen. The diet consisted of condensed milk, meat, and rice. The results of this huge over-nourishment of the dog are epitomized in the following table:

THE INFLUENCE OF OVERNUTRITION ON THE METABOLISM OF THE DOG

Period	Food	Body Wt.	R. Q.	Calories		
				24 Hr.	Per Kg.	Increase
		Kg.				Per Cent.
Basal	None	6.8	0.85	361	50.2	
Fasting, 5th day	"	5.9	0.73	300	50.0	
Interval of 9 days	160 cals. per kg.					
Maximal overnutrition, 1st day	202 cals. per kg. + 10.7 gm. N	6.8	1.15	666	92.5	82
Maximal overnutrition 10th day	202 cals. per kg. + 10.7 gm. N	10.1	1.17	847	87.3	75
Interval of 9 days	101 cals. per kg.					
Basal	None	9.7	0.89	506	53.3	7
Fasting, 16th day	"	7.2	0.73	364	50.5	

In this interesting experiment the summation effect of protein, carbohydrate, and fat, passing in large quantity into the blood stream, stands out clearly.

THE EFFECT OF GLUCOSE INGESTION COMBINED WITH LACTIC ACID OR ACETIC ACID

It is important to consider *the constancy of the metabolism under conditions of large carbohydrate ingestion.* This constancy of reaction is quite the same with the same dog as is to be observed after giving glycin (see p. 290). This appears in experiments which Lusk[1] instituted when he investigated the comparative influence of (*a*) 58 gm. of glucose, (*b*) 50 gm. of glucose plus 8 gm. of lactic acid, and (*c*) 50 gm. of glucose plus 3 gm. of acetic acid. The results for the 2d and 3d hours after giving these materials are indicated in the following table:

[1] Lusk, G.: J. Biol. Chem., 1921, **49**, 453.

DOG XIX AFTER GIVING DIETS ABOVE MENTIONED

Experiment No.	Date	State of Nutrition	Duration of Experiment	R. Q.	Calories	
					Indirect	Direct
	1920		Hr.			
47	May 13	Glucose.	2	1.01	44.56	42.17
50	" 20	"	2	1.01	44.71	43.66
Total.....			4		89.27	85.83
44	May 10	Glucose + lactic acid.	2	1.07	44.33	42.69
46	" 12	" " " "	2	1.02	44.39	41.29
Total.....			4		88.72	83.98
48	May 17	Glucose + acetic acid.	2	0.98	49.59	44.98
49	" 19	" " " "	2	0.97	49.76	45.42
Total.....			4		99.35	90.40

The close accord between the specific dynamic action of glucose and glucose plus lactic acid led Lusk to believe that lactic acid behaved as glucose does in metabolism. There is no evidence of an extra production of heat in order to convert it into glycogen. Its neutralization was probably accomplished in the intestine. To convert 8 gm. of lactic acid as lactate into glycogen would require 2.96 calories. To convert it into an oxidizable metabolite or into glucose requires less heat than this.

Acetic acid (R. Q. = 1), however, when given with the glucose solution, caused a marked increase in metabolism. Just as carbohydrate and fat, when given together, increase the metabolism by the sum of the effects which either alone would produce, so between carbohydrate and acetic acid there was a summation of effect. It is therefore evident that, if acetic acid be an intermediate of carbohydrate metabolism, it does not behave as does acetic acid which arises as the primary product of the β-oxidation of fatty acids. It may incidentally be remarked that, while lactic acid is convertible into glucose in the phlorhizinized dog, acetic acid is not convertible into glucose (see p. 640). Acetic acid does not change the carbon dioxid combining power of the blood, which indicates its rapid oxidation (see p. 299).

The evidence here presented contributes to emphasize the constancy of the reaction of the basal metabolism to the ingestion of food and of those metabolites which are fragments of food.

THEORIES OF METABOLISM

Rubner[1] conceived that the living cell had essentially two nutritive affinities—one for fat, the other for carbohydrate. When, as in diabetes, the affinity for carbohydrate was rendered inactive, fat alone oxidized for the maintenance of the body. Rubner's theory of metabolism is given on p. 287.

The more intimate knowledge derived from the study of the action of intermediary metabolites during short periods of time somewhat changes this theory. In presenting his interpretation of the specific dynamic action in the last edition of this book, the writer was keenly aware of the transitory character of all theories.[2]

In each mammal there is a *basal metabolism.* This corresponds with the minimal heat production eighteen hours after taking a mixed diet. Under these circumstances the cells are nourished by a food supply of fat and of carbohydrate, the latter supply being regulated by the liver. The basal metabolism may be acted on by food in the following ways:

(1) *Amino-acid stimulation,* in which some metabolites derived from protein stimulate the cells to a higher level of oxidative activity.

There are different ideas concerning the method of this action:

(*a*) Oxy- or keto-acids derived from protein metabolism directly stimulate the protoplasm of the cells leading to a greater oxidation, just as keto-acids derived from the oxidative deamination of protein are powerful stimuli to activity in the yeast cell in alcoholic fermentation.

(*b*) Oxy-acids, such as pyruvic acid formed from the oxidative deamination of alanin, require energy in considerable amount in order to convert them into glucose.

Neither of these conceptions can be neglected.

A fundamental consideration which will be discussed in a later chapter is that the heat of the specific dynamic action of protein cannot be used in the service of muscular work.

[1] Rubner, M.: Arch. f. Hyg., 1908, 66, 15.

[2] During the discussion which followed the presentation of papers on the subject of the specific dynamic action of the food-stuffs at the International Congress of Hygiene and Demography held at Washington in 1912, Professor Rubner said: "Ich freue mich dass die Frage der 'specific dynamic action' durch neue Untersuchungen weiter geführt worden ist. Die Erklärungen der Tatsachen wechseln mit der Zeit: das ist die Geschichte der Wissenschaft. Ich freue mich constatieren zu können, dass meine alten Untersuchungen nun endlich bestätigt worden sind."

It is possible that the specific dynamic action of protein is an exclusive function of the liver.

(2) *Fat plethora*, in which an influx of fat from the gut increases the heat production at the expense of fat itself. When fat is oxidized two carbon atoms are broken from the chain together. What form this cleavage takes is not known; it is usually pictured as productive of acetic acid. If palmitic acid broke up by successive oxidations into acetic acid radicles, one could write the following reaction:

$C_{16}H_{32}O_2$	+	$14O$	=	$8C_2H_4O_2$
Palmitic acid				Acetic acid
1 gram			=	1.348 grams
9353 calories			=	4706 calories

Such a reaction involves 50 per cent. loss of heat. Perhaps the energy imparted to the cell in fat metabolism is derived from a two-fold source—acetic acid and the oxidation at the β-carbon atom of the fatty acid; or perhaps a substance more highly explosive than acetic acid is set free as the result of β-oxidation. In any event one may conceive of the oxidation of fat as being in the nature of successive ultra-micro explosions, which act as power for the machinery of the cells.

(3) *Carbohydrate plethora*, in which an influx of carbohydrate from the intestine increases the heat production. When these enter the circulation alone they are oxidized to the exclusion of fat. It appears certain that the intermediary metabolites of glucose and fructose are far more readily oxidizable than fat, and on this account, when they are present, they satisfy the energy requirements of the cell and the fat is not attacked. If, perchance, glucose breaks up into methylglyoxal and this into acetaldehyd and formic acid, the reaction would be as follows:

$C_6H_{12}O_6—2H_2O \longrightarrow$	$2C_3H_4O_2 + 2H_2O \longrightarrow$	$2CH_3.CHO + 2HCOOH$
Glucose	Methyl-glyoxal	Acetaldehyd[1]
1 gram		0.4889 gram
3.762 calories		3.098 calories

[1] If the hydrogen in formic acid were oxidized to water ($HCOOH \longrightarrow CO_2 + H_2$, $H_2 + O = H_2O$) the heat evolved would be 0.755 calorie. The heat of combustion of formic acid is unknown.

And if the acetaldehyd were oxidized into acetic acid the reaction would be:

CH_3CHO	+	O	=	CH_3COOH
0.4889 gm.				0.6666 gm.
3.098 cals.				2.327 cals.

According to this schedule, of the original content of energy in glucose, the different metabolites would contain the following relative quantities:

	Gm.	Calories Per Cent.
Glucose	1	100
Formic acid	0.511	21
Acetaldehyd	0.489	79
Acetic acid	0.667	62

There is no indication of a physiologic separation of these varieties of energy.

It happens frequently that with the cessation of glucose absorption the respiratory quotient remains at 1.00, indicating that carbohydrate is still the essential food, and yet the metabolism has fallen to the basal level. One must, therefore, conclude that the metabolism increases only in the presence of a *plethora* of dissociated fragments of sugar. The metabolism may rise to a certain height which is not transcended, and an excess of metabolites above this level may be converted into fat (see p. 394) with scarcely any energy loss.

Muscular exercise may interfere with the formation of fat in the body by using the surplus of inflowing carbohydrate (see p. 398).

If muscular work is accomplished during carbohydrate absorption the incoming carbohydrate molecules may be used in the service of the muscles, and there being no excess or plethora of these molecules, carbohydrate may exert no specific dynamic action. Under these circumstances the calories of the basal metabolism plus the calories due to work are essentially the same whether or not carbohydrate is administered.

It is possible that a part of the specific dynamic action of carbohydrate is due to intermediary cleavages and the re-synthesis of the intermediates (see p. 383).

(4) *Carbohydrate and Fat Plethora.*—Here there is a summation of effect. It seems as though that part of the cell mechanism which is susceptible to fat metabolism *when fat is present in excess* is not inhibited from metabolizing such surplus fat even in the presence of carbohydrate.

(5) *Amino-acid Stimulation and Carbohydrate and Fat Plethora.*—Simultaneous ingestion of an amino-acid and carbohydrate acts in such a manner as to suggest that the increase in metabolism due to carbohydrate plethora is essentially independent of that due to the

chemical stimulus of amino-acids. Also when an amino-acid is given together with glucose at the height of fat metabolism (four hours after fat ingestion) the increase in heat production is nearly one amounting to a summation of the three influences.

One may, therefore, conclude that the influence of food upon the quiet resting cell under these circumstances is upon three independent mechanisms within the cell:

(1) A mechanism which is receptive to a chemical stimulus derived from the metabolism of such amino-acids as glycin and alanin, or one which receives a quantum of energy derived from the intermediary conversion of such amino-acids into glucose.

(2) A mechanism of carbohydrate plethora which allows the metabolism of carbohydrate up to the limits imposed by "self-regulation." Energy derived from the intermediary breakdown of carbohydrate or absorbed in the intermediary synthesis of the metabolites into glucose or glycogen may here be a contributing factor.

(3) A mechanism capable of receiving power from that quota of fat which when in excess increases the heat production of the cell.

THE CONVERSION OF CARBOHYDRATE INTO FAT

Voit, when he wrote his "Physiologie des gesammt Stoffwechsels und der Ernährung," in 1881, was unable to give definite proofs of the conversion of carbohydrate into fat in the organism, although such conversion was popularly believed to take place. Definite proof of the conversion of carbohydrates into fat was afforded by Meissl and Strohmer,[1] who gave a hog, weighing 140 kilos, 2 kilograms of rice containing 1592 grams of starch daily for seven days, and collected the carbon and nitrogen of the excreta by means of a Pettenkofer-Voit apparatus during two days of the period. The average results per day were as follows:

	Carbon, Grams	Nitrogen, Grams
Ingested in food	765.37	18.67
Excreted	476.15	12.59
Balance retained in the body	289.22	6.08

The nitrogen retained represented 38 grams of protein containing 20.1 grams of carbon; 269.12 grams of retained carbon were therefore

[1] Meissl, E., and Strohmer, F.: Sitzungsber. d. k. Akad. d. Wissensch., 1883, **88,** III Abth.

available for glycogen or fat construction. Since the amount of carbon retained exceeded the possible glycogen formation, fat must, therefore, have been added to the body. Had all the carbon retained been converted into fat it would represent a production of 343.9 grams of fat. Of this only 33.6 grams of fat could have arisen from the protein metabolism of the period. Hence it is possible that 310.3 grams of fat may have originated from 1592 grams of starch ingested, which indicates a conversion of 19.5 per cent. of the starch given into fat.

Similar experiments were made with geese by E. Voit and C. Lehmann.[1] The geese were starved four and a half days and were then fed with rice.

One of these respiration experiments which lasted thirteen days has been published,[2] and is as follows:

	Nitrogen, Gm.	Carbon, Gm.
In the 2609 grams of rice	41.47	1159.7
In the excreta—		
Urine and feces	45.39	134.8
Respiration	.....	657.8
Total	45.39	792.6
Change in the body	−3.92	+367.1

At the commencement of the experiment the animal weighed 4 kilograms. There was no protein retention, but 31 per cent. of the carbon ingested was not eliminated. The protein metabolism could not yield nearly enough carbon to account for that retained. As the rice contained but 0.51 per cent. of ether extract, the retained carbon could not have been administered in the form of fat. If 367.3 grams of carbon had been retained in the form of glycogen this would have aggregated 851 grams, or 20 per cent. of the whole goose, or in per cent. the starch content of a potato. This is a manifest impossibility, since E. Voit[3] found only 2.2 per cent. of glycogen in a goose which had been largely fed on rice. Since the carbon retained could not have been stored as glycogen, the only alternative remaining is to assume its retention as fat.

Rubner about the same time showed the same principles to be true in the case of the dog. It is evident, then, that pigs, geese, and dogs can convert carbohydrates into fat. The fattening of cattle

[1] Voit, C. v.: Sitzungsber. d. kgl. bayr. Akad. d. Wissensch., 1885, p. 288.
[2] Lehmann, K. B., and Voit, E.: Z. f. Biol., 1901, **42**, 644.
[3] Voit, E.: *Ibid.*, 1889, **25**, 543.

may be similarly accomplished. The ability to convert carbohydrate into fat probably exists throughout the animal kingdom.

When carbohydrates are converted into fat in the organism the respiratory quotient ($\frac{\text{Volume } CO_2}{\text{Volume } O_2}$, see p. 62) may rise very considerably above unity. This is for the reason that an oxygen-rich substance like glucose is being converted into substance which is poor in oxygen. Hence the volume of expired carbon dioxid may be greater than the volume of inspired oxygen. Max Bleibtreu[1] found that the respiratory quotient of a goose which had been stuffed with grain was 1.33, whereas the same goose when fasting showed a normal quotient for that condition of 0.728. Pembrey[2] describes how marmots previous to the winter hibernation instinctively devour large quantities of carbohydrate food, and how the respiratory quotient may rise even as high as 1.39. This indicates a fat production for use during the winter.

Grafe[3] gave to a fasting dog three times his daily caloric requirement of energy in the form of carbohydrate, and noted an increase of 33 per cent. in the heat production and a maximal non-protein respiratory quotient of 1.31. A discussion of the intermediary chemical reactions involved in this process has already been given (see p. 350). Written in their simplest formulæ the production of butyric or of palmitic acids from glucose would read:

$$C_6H_{12}O_6 + O_2 = C_4H_8O_2 + 2CO_2 + 2H_2O$$
$$4C_6H_{12}O_6 + O_2 = C_{16}H_{32}O_2 + 8CO_2 + 8H_2O$$

One may accept Bleibtreu's formula as the simplest expression of the conversion of carbohydrate into fat, as follows:

270.06 gm. glucose = 100 gm. fat + 115.45 gm. CO_2 + 54.6 gm. H_2O
1014 calories = 950.0 calories 58.78 liters

Magnus-Levy[4] made a similar calculation. On account of a kindly criticism of Boothby a higher caloric value is given for glucose than in the last edition of this book. The reaction is evidently exothermic, 6.3 per cent. of the heat being liberated. If the heat evolved be measured on the basis of the extra carbon dioxid production, 1 liter of such carbon dioxid would have a value of 1.09 calories, or less than one-sixth the caloric equivalent of a liter of carbon dioxid obtained from the oxidation of glucose in the ordinary manner.

[1] Bleibtreu, M.: Pflüger's Arch. gesam. Physiol., 1901, **85**, 345.
[2] Pembrey, M. S.: J. Physiol., 1901–02, **27**, 407.
[3] Grafe, E.: Deut. Arch. klin. Med., 1914, **113**, 1.
[4] Magnus-Levy, A.: Pflüger's Arch. gesam. Physiol., 1894, **55**, 103.

On the basis of this the heat production of a dog after taking 70 grams of glucose was calculated in experiments performed by Lusk.[1] The results of two of the three experiments are presented in the accompanying table:

DOG III. METABOLISM AFTER TAKING 70 GRAMS OF GLUCOSE IN 210 C.C. OF WATER AT 38°

	Experiment 88				Experiment 91			
Hours	Non-protein R. Q.	Indirect Uncorrected	Indirect Corrected	Direct	Non-protein R. Q.	Indirect Uncorrected	Indirect Corrected	Direct
		Calories	Calories	Calories		Calories	Calories	Calories
2	1.03	25.24	25.38	26.12	1.08	24.52	24.87	25.31
3	1.11	24.89	25.40	25.83	1.14	24.91	25.54	25.63
4	1.12	24.82	25.35	24.86	1.16	24.98	25.67	25.12
		74.95	76.13	76.81		74.41	76.08	76.06

That the method of calculation of indirect calorimetry in the presence of respiratory quotients above unity is correct may be deduced from these experiments. The "uncorrected" heat values represent calculations based on the oxygen absorption alone, while the "corrected" values are those in which to a liter of CO_2 eliminated in excess of a non-protein respiratory quotient of unity is given a value of 1.09 calories. This value corresponds to the conversion of 4.60 grams of glucose (or 5.06 grams of starch) into 1.70 grams of fat.

It is evident that after a large ingestion of glucose direct and indirect calorimetry agree closely if the heat value of the carbon dioxid which is evolved in the intermediary transformation of carbohydrate into fat be taken into consideration.

During the first three hours of Experiments 88, 90, and 91 the calculated heat production was 75.81, 75.30, and 75.64, while the CO_2 excretion in excess of a non-protein respiratory quotient of 1.00 was 1.07, 0.80, and 1.53 liters; it is, therefore, apparent that the intensity of metabolism is not related to the height of the respiratory quotient. The transformation of carbohydrate into fat takes place with the liberation of very little energy, and the height of the total metabolism is scarcely affected by the process.

This work was extended by Rapport, Weiss, and Csonka[2] in experiments on a hog, a much more suitable animal for the demon-

[1] Lusk, G.: J. Biol. Chem., 1915, **20**, 555.
[2] Rapport, D., Weiss, R., and Csonka, F. A.: *Ibid.*, 1924, **60**, 583.

stration of fat production than is the dog. These experimenters found in a healthy young hog of stunted growth and weighing 25 kg., in the diet of which the protein element had been notably restricted, that the administration of 300 gm. of starch and a liter of milk brought about the formation of fat from carbohydrate which continued vigorously for 21 hours or more. The respiratory quotient reached 1.25, and over half the calories of the diet were retained for growth. The maximum production of fat was 3.4 gm. per hour, and the average production was 2.5 gm. per hour or 61 gm. per day. It was noticed that during an hour of muscular exercise the respiratory quotient fell to 1.01. The excess of carbohydrate, which the hog had been converting into fat, was used in the service of the muscles.

The withdrawal of glycin from this hog by means of benzoic acid did not alter its heat production.

As the stunted hog gave such favorable results, Wierzuchowski and Ling[1] repeated the experiments upon another young hog under entirely normal conditions of nutrition. The basal metabolism of Hog II is given on p. 130. When starch and glucose were administered together the metabolism rose 100 per cent. above the basal level during the first four hours and fell thereafter to a level which was constantly maintained for at least 20 hours. The highest respiratory quotient recorded was 1.58, which is believed to be the highest ever observed. The respiratory quotient was maintained at about 1.40 during a period of about 20 hours following the ingestion of 700 gm. of starch. The maximum production of fat in a single hour reached 7.1 gm.; and for the 24 hour period 5.2 gm. per hour. At times the fat production from carbohydrate averaged 125 gm. *per day* or 0.9 per cent. of the body weight of the animal. Of the calories in the starch 27 per cent. was used to satisfy the basal metabolism, 13 per cent. for the specific dynamic action, and 56 per cent. was converted into fat.

When one attempts to picture the turbulence of the processes involved in this great production of fat from carbohydrate by that supreme converter of maize into animal fat, the American hog, one is surprised to find that the rate of fat production reaches a maximum of only 2 mg. *per second* and an average of 1.5 mg. per second in an animal weighing 13.5 kg. It is apparent that it will be a matter of extraordinary technic to intercept the metabolites here involved and

[1] Wierzuchowski, M., and Ling, S. M.: J. Biol. Chem., 1925, **64**, 697.

to determine what their reactions are in the process of fashioning fat from carbohydrate.

In a series of 12 hourly periods the heat production of the hog, calculated by the method of indirect calorimetry, was 426.5 calories and the "heat eliminated" by the hog (body temperature changes disregarded) was 426.8 calories, which affords a justification for the validity of the calculations.

The heat production from protein did not exceed 3 per cent. of the total heat production of the animal nourished under these conditions.

A table showing the metabolism of the hog during the hours immediately after the ingestion of 200 gm. of starch and 100 gm. of glucose is given below:

EFFECT ON HOG II OF TAKING 200 GM. STARCH AND 100 GM. GLUCOSE

Age	Time after Food	R. Q.	Fat from Carbohydrate per Hour	Heat Production	
				Per Hour	Increase over Basal
Days	Hr.		Gm.	Cal.	Per Cent.
100	3, 4	1.52	6.9	41.9	
104	2, 4, 5, 6	1.44	6.2	43.8	
106	2	1.34	4.8	42.6	
107	2, 3	1.37	5.2	42.4	
Average	.....	....	5.8	42.7	102

The constancy of the metabolism, irrespective of the variations of the respiratory quotient, is strikingly apparent.

According to Ellis and Hankins[1] the hog produces "hard pork" from carbohydrate manufacture, whereas "soft pork" arises from ingested fats, such as that of the peanut and the like.

[1] Ellis, N. R., and Hankins, O. G.: J. Biol. Chem., 1925, **66**, 101.

CHAPTER XVII

THE INFLUENCE OF MECHANICAL WORK ON METABOLISM

We are so accustomed to investigate the functions of different organs or parts of the body that we do not see the individual as a living whole. Some of the mental disturbances of orthodox scientists depending upon this defect are very interesting phenomena.—STEWART PATON.

In the account of metabolism during starvation a short description has already been given of the influence of mechanical work on protein metabolism, of the influence of posture on general metabolism, and of the relation of the amount of metabolism to the diurnal variations of human temperature.

The source of mechanical work must be from metabolism, for mechanical energy cannot be derived from nothing. The necessary energy might be obtained in one of two ways, either at the expense of a proportionate reduction in the quantity of heat liberated by the resting organism, or by an increase in the amount of the metabolism. In the former case work would diminish the heat production and might cool the tissues, which is not observed to take place. If work were done at the expense of increased metabolism, and if this increase were completely converted into mechanical effect, then the heat production in the organism might remain the same as in the resting state. If, however, the result of mechanical effort be a stimulation of metabolism to the extent of not only enabling the body to do work but also causing it to produce more heat than when at rest, then the tendency of the tissues must be to grow warmer, perhaps with a resulting outbreak of sweat to reduce the body temperature through physical regulation. The last named is the actual process.

Lavoisier's discovery that the absorption of oxygen is increased during mechanical exercise firmly established the fact of a higher metabolism under these conditions.

The first experiments in which the effect of work upon the total metabolism was demonstrated were made upon a man by Pettenkofer and Voit.[1] A man turned an ergostatic wheel 7500 revolutions on each working day for a period of nine hours, which afforded sufficient

[1] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1866, 2, 537.

exercise to cause great fatigue at the end of the day. The experiments were made both during hunger and when the man was ingesting a medium mixed diet. The food supplied in the mixed diet contained:

	Grams	Calories
Protein	121.7	506
Fat	117	1088
Carbohydrates	352	1443
Total		3037

The metabolism of this man, a strong workman, weighing 70 kilograms, at rest and at work, starving or on the medium mixed diet as given above, is presented in the following table:[1]

EFFECT OF MECHANICAL WORK ON METABOLISM IN MAN

	Grams Metabolized			Cal. of Metabolism	Cal. above Fasting Quantity	Experiment No. of Pettenkofer and Voit
	Protein	Fat	Carbohydrates			
Starvation—Rest	70.8	222	...	2374	....	I
" —Rest	68.7	208	...	2231	....	III
" —Work	66.1	387	...	3882	1582	IV
Mixed diet—Rest	121.7	73	352	2638	336	V
" —Rest	118.7	93	352	2714	412	VI
" —Rest	125.0	84	352	2750	458	VII
" —Work	121.7	208	352	3856	1554	VIII
" —Work	122.0	152	352	3378	1076	IX

From these early experiments it was evident that mechanical work did not increase protein metabolism even in starvation, but that the power to do work might readily be supplied by the increased metabolism of fat.

The experiments of Atwater and Benedict[2] were the first to demonstrate exactly that mechanical work was done at the expense of a dynamic equivalent of metabolism—a splendid confirmation of the law of the conservation of energy.

Thus J. C. W., during two periods of twenty-two days each, ingested day by day diets which produced the following metabolism as calculated from the body's excreta:

[1] I have multiplied the nitrogen of the ingesta and excreta by 6.25 to obtain the quantity of the protein given and metabolized. The ratio N:C = 1:3.28 in protein has been employed. The dry starch has been calculated as containing 44.2 per cent. and the fat as containing 76.5 per cent. of carbon, which were the figures used by Pettenkofer and Voit. Rubner's standard calorimetric values have been used. (See Introductory Chapter.)

[2] Atwater, W. O., and Benedict, F. G.: "Experiments on the Metabolism of Matter and Energy in the Human Body," U. S. Dept. of Agriculture, Bull. 136, 1903.

CALCULATED METABOLISM

	Period I Carbohydrate Diet	Period II Fat Diet
Protein	434 calories.	489 calories.
Fat	1288 "	3190 "
Carbohydrates	3371 "	1465 "
Total metabolism	5093 "	5144 "

The average of work accomplished and body heat evolved each day, as measured in the Atwater calorimeter, were as follows:

WORK AND METABOLISM AS DIRECTLY MEASURED

	Carbohydrate Diet	Fat Diet
Mechanical work	543 calories.	550 calories.
Body heat	4593 "	4555 "
Total metabolism	5136 "	5105 "

The work was done on a stationary bicycle. It is evident that the work could not have been at the expense of protein metabolism; but it is also plain that the work could have been derived from carbohydrate combustion, even in the "fat" diet of Period II.

In one other experiment Atwater and Benedict calculated for J. C. W. a metabolism amounting to 9981 calories, divided as follows: Protein, 478 calories; fat, 7744 calories; carbohydrates, 1759. The man worked for sixteen hours on the bicycle. The work done measured an equivalent of 1482 calories; the body heat production was 7382 calories, both of which were measured in the Atwater calorimeter, and the total energy loss reached 9314 calories,[1] a height of metabolism attained also by Maine lumbermen[2] actively employed (see p. 463).

The Influence of Mechanical Work on the Metabolism of Protein.— In the classical experiments of Fick and Wislicenus it was established that the power of the working muscle could not possibly be derived from the energy liberated by the metabolism of protein alone.

Fick and Wislicenus[3] climbed the Faulhorn, in Switzerland, a mountain 1956 meters high. The product of their weight into the height to which they raised themselves gave them a close approximation to the amount of the work done. The experimenters took their last nitrogenous food seventeen hours before starting on their walk. They climbed for six hours and collected the urine of this period and that of seven hours thereafter. Their results were as follows:

[1] The calories calculated from the metabolism and those directly measured by the calorimeter did not exactly agree in this particular instance—an exception in a brilliant series.

[2] Woods, C. D., and Mansfield, E. R.: U. S. Dept. of Agriculture, Of. of Exp. Sta., Bull. 149, 1904.

[3] Fick, A., and Wislicenus: "Myothermische Untersuchungen," Wiesbaden, 1889.

	Urinary N of 13 Hours, Grams	Dynamic Value of N in Kg.-m.	Body Weight, Kg.	Height of Faulhorn	Work in Kg.-m.
Fick	5.74	63,378	66	1956 meters.	129,096
Wislicenus	5.54	61,280	76	1956 "	148,656

The work accomplished represents three times the energy liberated from the protein metabolism of 13 hours. The output of energy as measured above was not all the increase in the amount of mechanical energy during the period, for the heart and respiratory muscles acted with greater force, and energy was expended by swinging the arms and by friction on the road.

The observation of Pettenkofer and Voit that protein metabolism is not appreciably affected by muscular work has often been challenged. While I was in Voit's laboratory he gave this problem to a medical student named Schnabelmeyer. This man partook of a constant diet the basic principles of which consisted of finely chopped sterilized ham, zwieback, and butter, administered for a week at a time. One day, the 4th of the week, was devoted to exercise. In a first experiment the exercise consisted of running several hours through the streets of Munich; in the 2d a tower of the *Frauenkirche*, 355 feet in height, was climbed 15 times. The experimental results were never published because the subject acquired so violent a distaste for the diet that he refused to go on. I mention this because I overheard the professor say of them, "Es ist klar man muss die alle feinste Methoden benützen."

The problem was next given to Krummacher.[1] A porter, weighing, 79 kilograms, partook of a diet containing 3700 calories, 14.28 grams of protein nitrogen, and a large amount of carbohydrate. The man turned a dynamometer and produced 402,000 kilogrammeters of work. The slight increase in protein metabolism could have yielded but 3 per cent. of the energy required for the work. Krummacher states that protein metabolism may increase during work only when the non-nitrogenous fat and carbohydrates become less available in metabolism. We have already seen that protein metabolism rises in the absence of carbohydrates. It may be that with the exhaustion of carbohydrates during exercise a period ensues when the loss of their influence leads to an increased protein destruction.

[1] Krummacher, O.: Z. f. Biol., 1896, **33**, 108.

The larger the quantity of carbohydrates given, the less marked would be this influence. It is interesting in this connection that soldiers when starting on a march may have a high respiratory quotient (indicating the combustion of carbohydrates), which falls at the end of the march (fat combustion) and which may remain lower than at first, even on a day following the march.[1] The fact that mechanical work may be accomplished at the expense of an increased combustion of fat and carbohydrates should not cause one to forget that protein *may* become the sole source of energy in the body. It has already been shown that a fasting animal, after burning all its fat, may maintain its life on protein alone (see p. 108), and that Pflüger kept a dog in active condition on meat alone. As protein may yield 58 per cent. of sugar this substance may still be the principal source of energy.

The validity of the proposition that muscular work has no influence upon protein metabolism has been strongly challenged by Cathcart[2] who marshals much evidence against it. He cites four experiments accomplished in his own laboratory. The subject partook of a constant dietary during each period and on the working days performed with his arms for a period of one hour the equivalent of 25,000 kilogrammeters of work upon an ergometer. The diet contained 3000 calories, and the nitrogen output was as follows:

EFFECT OF WORK UPON THE OUTPUT OF TOTAL NITROGEN
(Average of 3 experiments for each diet)

	Diet I	Diet II	Diet III	Diet IV
	Gm.	Gm.	Gm.	Gm.
Pre-work (average 4 days)	8.78	17.31	17.40	14.30
Work (average 6 days)	10.01	19.96	18.23	15.44
Post-work (average 4 days)	9.05	17.76	17.34	16.34

These are the results of averages of three experiments with each diet.

Campbell and Webster[3] report that a man expending 100,000 kg.-m. of work upon a stationary bicycle, an amount signifying a severe strain, eliminates 10.25 gm. of urinary nitrogen on the day of work, in contrast with 8.01 gm. on the preceding day of rest; also that the creatinin nitrogen rises from 0.74 gm. to 0.93 gm.

[1] Zuntz, N., and Schumburg, H.: "Studien zu einer Physiologie des Marsches," Berlin, 1901.
[2] Cathcart, E. P.: Physiol. Rev., 1925, **5**, 225.
[3] Campbell, J. A., and Webster, J. A.: Biochem. J., 1922, **16**, 106.

In a report by Garry[1] it is stated that an hour of static work, such as pulling against powerful springs, may produce fine fibrillary tremors in the muscle substance followed by fatigue lasting 4 hours. When this work was performed by a man whose diet was free from purins, both the uric acid nitrogen and the total nitrogen in the urine were slightly increased, as appears below:

	Urine N	
	In Uric Acid	Total
	Gm.	Gm.
2 days before work	0.151	14.64
1 " " "	0.152	14.70
Work day	0.158	14.77
1 day after work	0.163	14.83
2 " " "	0.158	14.64
3 " " "	0.153	14.60

Coinciding with this, the papers of Rakestraw[2] demonstrate an increase in the uric acid of the blood in nine men who ran up and down stairs rapidly for 10 minutes or until completely exhausted.

The experiments of Cathcart come into apparent conflict with experiments on dogs. Atkinson[3] gave to a dog weighing 10.5 kg. 600 gm. of meat daily and collected the urinary nitrogen during the 4th, 5th, and 6th hours after administering the food. In six experiments the dog was caused to run on a treadmill during the 5th hour a distance of 1.32 miles (2125 meters) for half an hour. The urinary analyses showed the following results:

	N in Urine per Hour		
	4th Hr.	5th Hr.	6th Hr.
	Gm.	Gm.	Gm.
Resting, average of 6	1.04	1.08	1.07
Work, 5th hr., average of 6	1.05	**1.07**	1.07

It appeared to be certain from these experiments that mechanical work had no influence on the hourly rate of absorption of protein or on the intensity of the hourly metabolism of protein in a dog that had received meat in large quantity.

Another series of experiments was performed by Chambers and Milhorat,[4] this time upon fasting dogs. The dogs ran on a treadmill

[1] Garry, R. C.: J. Physiol., 1926–27, **62**, 364.
[2] Rakestraw, N. W.: J. Biol. Chem., 1921, **47**, 565; 1923, **56**, 121.
[3] Atkinson, H. V.: *Ibid.*, 1918, **33**, 379.
[4] Chambers, W. H., and Milhorat, A. T.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1927, **81**, 469.

for 2 miles for half an hour during 3 consecutive hourly periods. The urine was collected during 3 hourly periods before the hours of exercise and hourly during the periods of exercise. In a previously well-nourished dog, on the 3d or 4th day of the fast there was always an extra output of nitrogen during the hours of work and of post-work. In one case there was an increase of 55 per cent. On the 10th day of fasting and thereafter a condition was reached in which muscular work no longer produced an increase in protein metabolism. Values for pre-work hours of 49, 47, and 50 mg. of nitrogen were obtained, in contrast with 48, 50, and 48 mg. during the hours of work. The authors believe that the rise in protein metabolism during work in the early days of fasting is associated with the dislodgment of deposit protein, or the break-up of an amino-acid-glycogen compound in the body, (see p. 642) and they question the idea that the fundamental wear and tear quota of protein metabolism is affected by mechanical work.

Perhaps a reconciliation of the various points of view may be effected along these lines.

The following experiment not only indicates the point that muscular work does not increase protein metabolism, but it also shows that *the character of the protein metabolism is unchanged by ordinary muscular activity*. Shaffer[1] has given a man a diet which was free from purins and which contained only 5.9 grams of nitrogen. The individual spent the greater part of six days in bed as a rest period (I). He then occupied himself for five days with laboratory work, which gave a normal period (II). During a final period (III) of four days he worked in the laboratory and performed in addition such mechanical work as that of walking 10 miles. The average of the analyses of the urines of the three periods are given below:

UNCHANGED CHARACTER OF THE URINE AFTER MUSCULAR WORK

Period	Food		Urine Values in Gm.					
			Nitrogen as:					Sulphur
	N Gm.	Calories	Total	Ammonia	Creatinin	Uric Acid	Rest	Total
I. Rest	5.9	2300	4.77	0.35	0.605	0.11	0.35	0.438
II. Normal	6.0	3000	4.40	0.38	0.60	0.106	0.42	0.424
III. Work	5.9	3200	3.94	0.42	0.56	0.12	0.42	0.414

[1] Shaffer, P. A.: Am. J. Physiol., 1908, **22**, 445.

Shaffer concludes that if sufficient food be allowed, an increase or decrease of muscular activity has no effect on protein metabolism as indicated by the various quantities of nitrogenous end-products which appear in the urine. Shaffer agrees with Van Hoogenhuyze and Verploegh[1] that with adequate nourishment the creatinin elimination is unaffected by muscular work.

Kocher[2] states that doubling the heat production of the day as brought about by walking 60 kilometers (37.5 miles), *i.e.*, from Munich to the Starnberger See and back, has little or no influence upon the protein metabolism of men, whether the diet consists of starch, sugar and cream, or of meat and fat without carbohydrates.

Bornstein[3] reports continual retention of ingested protein during seventeen days' work, at a time when only protein was administered. The quantity of protein given was large, containing 19.96 grams of N, and the daily work accomplished was moderate, being 17,000 kilogrammeters. The nitrogen retention amounted to 1.475 grams daily, or an addition of 800 grams of "flesh" to the body in seventeen days.

Loewy[4] reaches the same conclusion that long-continued muscular exercise favors protein retention. This suggests the basis of muscular hypertrophy due to physical exercise.

Large protein ingestion, however, is not apparently essential to the full maintenance of physical power. This has been shown by Chittenden,[5] who maintained soldiers and athletes in physical training for months at a time on diets containing between 7 and 10 grams of nitrogen, or about half what the average man takes if the decision be left to his taste (see p. 451).

It is evident that the power to accomplish muscular work is not usually derived from protein metabolism, but from the combustion of the non-nitrogenous sugar and fat. Therefore, physical exercise requiring fat consumption without concomitant destruction of protein must be of the greatest value in the treatment of obesity.

On the other hand, there is no evidence to show that the ingestion of meat in large quantity lessens the physical efficiency. Experiments to test this were made by Bassett, Holt, and Santos[6] upon four individuals. Periods of a week, during which no or very little meat

[1] Van Hoogenhuyze, C. J. C., and Verploegh, H.: Z. physiol. Chem., 1905, **46**, 415.
[2] Kocher, R. A.: Deut. Arch. klin. Med., 1914, **115**, 82.
[3] Bornstein, K.: Pflüger's Arch. gesam. Physiol., 1901, **83**, 540.
[4] Loewy, A.: Arch. f. Physiol., 1901, p. 299.
[5] Chittenden, R. H: "Physiological Economy in Nutrition," New York, 1904.
[6] Bassett, S. H., Holt, E., and Santos, F. O.: Am. J. Physiol., 1922, **60**, 574.

was taken, were compared with periods when a luncheon containing 300 gm. of meat with bread and potatoes was served to each of them in the laboratory. (The war ration of a French or Italian soldier in the field is 300 gm. of meat per day.) The subjects were instructed to walk a given distance both morning and late afternoon on their way to and from the college, striving to accomplish the distance in the shortest possible time. The weather was cool, and the subjects were equipped with pedometers. On the completion of the walk the pulse was counted and then the time noted until the pulse rate became normal once more. This has been suggested by Lewis, Cotton, and Rapport[1] as a test for physical fitness. The results obtained from one subject are given below:

	Low Protein Week	High Protein Week
Average number of steps per day	19,691	20,880
Urine N, average grams	8.0	16.9
N grams, maximum; minimum	8.8-6.9	19.4-15.8
Time of test walk, in minutes	27.5	27.5
Time per 1000 steps, in minutes	7.4	7.4
Pulse: End of exercise	117	114
After 4 minutes	82	78
After 5 minutes	75	75

The results showed (*a*) that the presence or absence of meat from the dietary during periods as long as one week had no demonstrable effect upon the capacity for doing an amount of work so graded as to reach the limit of the physical capacity during a short period of time; (*b*) removal of meat from the dietary for a period of one week did not diminish the sense of well-being; (*c*) there was a distinct and uniformly present sense of sleepiness for 2 or 3 hours during the afternoon following the ingestion of 300 gm. of meat at luncheon.

MUSCLE WORK AND THE SPECIFIC DYNAMIC ACTION OF PROTEIN

In the earlier editions of this book (1906 and 1909), the question was asked whether energy evoked by the specific dynamic action of the food-stuffs could be utilized in the production of mechanical work.

The following experiments by Rubner[2] show beautifully that *there is a summation of function as regards the extra heat production*

[1] Lewis, T., Cotton, T. F., and Rapport, D. L.: Med. Res. Com. Special Report Series No. 8, London, 1917, p. 26.

[2] Rubner, M.: Sitzungsber. d. preuss. Akad. d. Wissensch., 1910, **16**, 316.

due to the specific dynamic action of protein and the extra heat production incident to mechanical work:

THE INFLUENCE OF DIET AND MECHANICAL WORK UPON THE METABOLISM OF A MAN 61-63 KG. IN WEIGHT

Diet and Conditions	Heat Produced			Heat Lost		
	Twenty-four Hours	Increase	Increase Due to Work	Evap. H_2O	Rad. and Cond.	Work
	Calories	Per Cent.	Calories	Calories	Calories	Calories
No food, rest	1976	.....	....	380	1596	
Cane-sugar 600 gms. + H_2O 3000 gms., rest	2023	+ 2.4	....	529	1494	
Same + work (100,000 kg-m.)	2868	+45.2	845	907	1727	234
Protein, large amount of meat, rest	2515	+27.2	....	614	1901	
Protein, same diet, + work (100,000 kg.-m.)	3370	+70.5	855	1235	1901	234

Rubner observed that mechanical work was performed with greater ease when cane-sugar was the basis of the diet than when protein was given. The temperature of the chamber in which the experiments were performed was about 20° and the humidity was about 40 per cent. Rubner calls especial attention to the fact that when cane-sugar was given the increased heat produced by the body was lost, partly by the increased evaporation of water (62 per cent. of the increased heat production) and partly by an increase in radiation and conduction from the skin (38 per cent. of the increased heat production), whereas after meat had been given the elimination of the entire extra heat production due to work was thrown upon the activity of the sweat-glands. A high protein dietary is therefore contraindicated in athletic contests, especially when the weather is hot and humid.

The 100,000 kilogrammeters of work described above were produced by the action of the arms upon an ergostat. Since this quantity of work is the mechanical equivalent of 234 kilo-calories, and since 850 extra calories of metabolism were invoked in its accomplishment, it is evident that the mechanical efficiency of the human engine under these circumstances was $\frac{234}{850}$, or 27.5 per cent.

Benedict and Murschhauser[1] confirm the summation of energy increase from food and work in the case of men walking in a horizontal direction.

[1] Benedict, F. G., and Murschhauser, H.: "Energy Transformations during Horizontal Walking," Carnegie Institution of Washington, Pub. 231, 1915, p. 91.

These results of Rubner upon man were confirmed by Anderson and Lusk[1] with a dog which ran on a treadmill placed in the small respiration calorimeter of the Cornell University Medical College.

In six different experiments the dog ran for 3 hours, beginning 18 hours after the ingestion of the last standard maintenance diet, at rates of between 2.48 miles (3925 meters) and 2.98 miles (4806 meters) per hour. The average respiratory quotient was 0.78 (maximum 0.81; minimum 0.75). The calories of the basal metabolism (17.2 to 17.5 calories per hour) were deducted from those produced during working periods. The dog varied in weight between 8.0 and 9.4 kg. The heat production varied between 60.8 and 76.7 calories during the hours of the periods of work.

The amount of energy produced above the basal requirement was the quantity necessary for the accomplishment of the work done. *In the six experiments the energy equivalent of* 0.580 *kilogrammeter of work was necessary to move* 1 *kilogram of the dog's body weight* 1 *meter with a maximum variation of* ±1.7 *per cent.* This notwithstanding the fact that the weight of the dog varied 17 per cent. and the rate traveled varied 20 per cent. in the several experiments.

The results are presented in the following table:

THE INFLUENCE OF MECHANICAL WORK 18 HOURS AFTER FOOD INGESTION

Date	Experiment No.	Weight of Dog	Indirect Calorimetry	R. Q.	Work in Distance Traveled		Calories above the Basal per 1000 Meters Traveled	Work in Kg.-M. to Move 1 Kg. 1 Meter
1917		Kg.	Cal.		Miles	Meters		
Jan. 5.....	2	8.0	60.8	0.78	2.48	3925	11.0	0.585
Feb. 28.....	8	9.0	70.0	0.81	2.67	4300	12.3	0.580
Mar. 13.....	18	8.9	74.8	0.75	2.90	4688	12.2	0.585
" 23.....	24	9.2	76.7	0.74	2.92	4717	12.6	0.582
" 27.....	27	9.4	76.7	0.81	2.92	4718	12.6	0.570
	13	9.0	76.1	0.79	2.98	4806	12.2	0.578
				0.78				0.580

Maximum variation = ±1.7 per cent.

It was noted that after giving 750 gm. of meat the heat production rose from a basal value of 17.2 to a value of 30.0 calories per hour. If one calculates the extra heat production of the dog running after

[1] Anderson, R. J., and Lusk, G.: J. Biol. Chem., 1917, 32, 421.

the ingestion of the meat on the basis of allowance for the separation of the specific dynamic action of protein, one arrives at the following results.

	Cals. of Metabolism	Deductions	Cals. Due to Work	Weight	Distance Traveled	Work to Move 1 Kg. 1 Meter
		Cals.		Kg.	Meters	Kg.-m.
No food.....	76.1	17.2	58.9	9.0	4806	0.578
Meat, 750 gm.....	92.4	30.0	62.4	9.6	4704	0.587

It is evident that *the energy of mechanical work is superimposed upon the quantum of energy evolved from the specific dynamic action of protein.* The two factors are completely separable entities. In the interpretation of the specific dynamic action of protein these facts should always be borne in mind. The behavior of carbohydrate is entirely different, as will be shown shortly.

Anderson and Lusk verified this principle by giving 20 gm. of alanin to the dog. Without subtracting the specific dynamic action of alanin 0.620 kg.-m. of energy were required to move 1 kg. of body weight 1 meter, but if the specific dynamic action of alanin was deducted in the computation then 0.583 kilogrammeter of energy was required. Alanin therefore acts in such a way that during a period of mechanical work there is a summation between the increment of extra heat due to its metabolism and the extra heat evolved for the production of work. Alanin, which is completely convertible into glucose, behaves in an entirely different manner from glucose in metabolism.

THE FUEL OF MUSCULAR WORK

It has already been set forth that mechanical work may have little or no effect upon protein metabolism. Protein itself may be resolved into glucose and β-oxybutyric acid, so that the question of the source of muscular power reduces itself to the consideration of behavior of metabolites of carbohydrate or of fat.

Zuntz,[1] from experiments made by Heineman, calculated that when carbohydrates predominate in a man's diet an amount of energy above the resting requirement is liberated which equals 9.33 small calories for every kilogrammeter of work accomplished, whereas,

[1] Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1901, **83**, 557.

when fat is given, 10.37 calories are liberated in the performance of the same amount and the same kind of work. The work was done by turning the wheel of an ergostat. Since one kilogrammeter is the mechanical equivalent of 2.35 small calories, it is evident that 25 per cent. of the total excess of energy developed by work is convertible into mechanical effect, the balance being dissipated as heat. Similar experiments made by Zuntz on himself showed that 9.39 and 9.33 calories of metabolism were liberated on a fat diet, 10.37 and 10.41 on a carbohydrate diet, when one kilogrammeter of work was accomplished.

The average of these early experiments may be expressed as follows:

	Calories Required to Move 1 Kg. Body Weight 1 Meter	
	Fat Diet	Carbohydrate Diet
Zuntz	9.36	10.39
Heineman	10.37	9.33
Average	9.87	9.86

There seemed to be little difference in the efficacy of the body as a machine, whether fat or carbohydrate was used as fuel.

Heineman[1] remarks that Chauveau's idea that fat must be first converted into sugar before being available for mechanical work can scarcely be valid, for such a conversion of fat carbon into sugar would entail a minimum loss of 29 per cent. of the energy available for mechanical work.

A series of experiments by Anderson and Lusk was performed upon a dog running on a moving treadmill, as already described (see p. 410). The energy production of the dog was determined while he was running (*a*) 18 hours after food ingestion, (*b*) immediately after the ingestion of 70 to 100 gm. of glucose, and (*c*) after prolonged starvation.

After 70 gm. of glucose alone were given to this dog the heat production rose about 3.2 calories or 20 per cent., and the respiratory quotients were about 1.05. When the animal ran in the calorimeter the results were as presented in the following table:

[1] Heineman, H. N.: Pflüger's Arch. gesam. Physiol., 1900, **83**, p. 476.

COMPARISON OF THE EFFECT OF THE SAME AMOUNT OF MECHANICAL WORK 18 HOURS AFTER FOOD AND DURING THE HOURS IMMEDIATELY FOLLOWING THE INGESTION OF GLUCOSE

Date	Experiment No.	Weight of Dog	Food	Indirect Calorimetry	R. Q.	Work in Distance Traveled		Calories above the Basal per 1000 Meters Traveled	Work in Kg.-m. to Move 1 Kg. 1 Meter
1917		Kg.		Cal.		Miles	Meters		
Jan. 5	2	8.0	No food.	60.8	0.78	2.45	3925	11.0	0.585
	3	8.35	Glucose, 70 gm.	62.3	0.98	2.44	3936	11.1	0.579
Mar. 15	19	9.6	" 70 "	77.1	0.92	2.96	4771	12.5	0.555
" 23	24	9.3	No food.	76.7	0.74	2.92	4717	12.6	0.582
" 26	26	9.7	Glucose, 100 gm.	76.8	0.95	2.94	4737	12.5	0.550

It is apparent from this table that when mechanical work is accomplished during the hours following a large ingestion of glucose the heat production is about the same as that recorded when the intestinal tract is free from food. However, if one considers the added weight of the glucose in solution, then one may conclude from the evidence that *the forward movement of the dog's own weight may be executed with even less expenditure of energy in the presence of abundant carbohydrate food than when no food is taken. With carbohydrate the energy requirement for the forward movement of* 1 *kg.* 1 *meter may be* 0.550 *kg.-m. and without carbohydrate* 0.580 *kg.-m.* It appears that after glucose ingestion mechanical work may be accomplished at the expense of 5 per cent. less energy than when glucose is not taken.

The respiratory quotients do not rise above unity in any of these experiments. To furnish 75 calories per hour in the form of glucose for the working dog would require the absorption of 20 gm. of glucose per hour, which probably transcends the absorbing power of the intestine. In consequence of this the particles of glucose entering the circulation are probably immediately utilized by the active muscles, there is no *carbohydrate plethora* in the blood, and the manifestation of the specific dynamic action of glucose does not occur.

In the early days of deer hunting in the Adirondacks dogs were fasted for 5 days before they were put on the scent of deer and this without any prejudice to the power of the animal. The dog of Anderson and Lusk, following a run of about 9 miles in 3 successive hours, on the 13th day of fasting, jumped out of the calorimeter unfatigued, ran around the room, and in friendly fashion pawed one of the observing staff.

The following data are significant of the fall in weight and basal metabolism during the fasting period:

	Normal	13th Day of Fast
Weight, kg	9.2	7.4
Basal metabolism, cals. per hr	17.2	12.4

The loss in body weight was 20 per cent., the decline in heat production 28 per cent.

The metabolism during the experimental hours when the dog ran 4700 to 5000 meters per hour may be thus epitomized:

	Non-protein R. Q.	Work in Kg.-m. to Move 1 Kg. 1 M.
3d fasting day	0.710	0.584
5th " "	0.722*	0.570
8th " "	0.719*	0.587
13th " "	0.713*	0.595
Average		0.584

* Last hour of mechanical work.

During the various days of fasting it requires an average energy equivalent of 0.584 kilogrammeter of work, with a maximum variation of $\pm$ 2.4 per cent., to move 1 kg. of the dog's body weight 1 meter on the treadmill, in contrast with 0.580 kg.-m. required for the well-nourished dog doing the same amount of work. Therefore it may be stated that *the quantity of energy required to accomplish a given amount of work is the same whether the dog is in the best nutritive condition or has lost 20 per cent. in weight after 13 days of fasting.*

By a reduction of body weight one may economize in the amount of energy necessary for the basal metabolism, one may economize in the quantity of food fuel necessary to move the lesser body weight, but if a given amount of work is to be done it can be accomplished only at the expense of a definite quantity of energy, irrespective of the body weight.

These principles, enunciated at the time of the World War, are of fundamental importance.

The non-protein respiratory quotients of the dog running on the 13th day were in successive hours 0.721, 0.717, 0.713. Zuntz and Loewy[1] give 0.713 as the respiratory quotient for human fat.

The slightly higher quotients of the first 2 hours might be accounted for by oxidation of not exceeding 1 gm. of glycogen, which might

[1] Zuntz, N., and Loewy, A.: "Lehrbuch der Physiologie des Menschen," Leipzig, 3d ed., 1920, p. 686.

easily have arisen from a small amount of extra glycogen stored in the animal. In the 3d hour there was no sign of the combustion of glycogen. If the reaction glycogen ⇄ lactic acid had been going on in the animal it was proceeding in a steady state without the oxidation of either component. *The most obvious interpretation of the results is that the energy of muscular contraction in fasting is afforded by the oxidation of fat.* Only 3 per cent. of the total metabolism could have arisen from protein. It is believed by some that fat must first be converted into sugar before it can be available as the source of muscular work. As this transformation would inevitably lead to a loss of energy and as such loss does not appear in the above-mentioned experiments, it seems inconceivable that the process occurs. One may reiterate the statement, the production of sugar from fat is a figment of the imagination.

Summarizing the work of Anderson and Lusk, the following results appear:

	Work in Kg.-m. to Move 1 Kg. Body Weight 1 Meter
18 Hours after food	0.580
Meat, 750 gm. (less specific dynamic action)	0.587
Alanin, 20 gm. (less specific dynamic action)	0.583
Glucose, 70 and 100 gm	0.550
Fasting, 3d to 13th days	0.584

Work, therefore, is accomplished at the same expenditure of energy whether a mixture of carbohydrate and fat is oxidized 18 hours after food or whether fat alone is oxidized in starvation. The constancy of the outcome is remarkable.

Under conditions of fat ingestion the cost of work would probably be the same as in fasting. Some day someone will compare the relative efficacy of glucose and fructose as food fuel for muscular work.

Important experiments of Krogh and Lindhard[1] on the relative value of fat and of carbohydrate as sources of muscular energy were carried out on man. These authors state that "In the three best series of experiments the net expenditure of energy per Cal. of technical work varies from about 4.6 Cal. when fat alone is catabolised (R. Q. = 0.71) to about 4.1 Cal. when carbohydrate alone is catabolised (R. Q. = 1). The waste of energy from fat is 0.5 Cal. or 11 per cent. of the heat of combustion of the fat."

[1] Krogh, A., and Lindhard, J.: Biochem. J., 1920, **14**, 290.

The following table is compiled from the data offered by Krogh and Lindhard:

R. Q.	No. of Determinations	Average Calories Necessary per Calorie of Work Done
0.728–0.740	3	4.68
0.751–0.797	7	4.53
0.804–0.846	15	4.50
0.851–0.895	8	4.42
0.903–0.950	11	4.33
0.951–0.974	4*	4.27

* R. Q. of 0.966 omitted from the average.

The authors suggest that carbohydrate is formed from fat and provisionally stored when the quotient is below 0.8 and that a corresponding transformation of carbohydrate into fat takes place when the respiratory quotient is over 0.9. But they add, "It is clear that our experiments cannot be used as evidence to prove that fat must be converted into sugar before being utilized for muscular work." Others, however, have so used them.

It is well known that man suffers from a higher degree of ketosis in the absence of carbohydrate food than the dog does. The condition of ketosis is not abolished until the respiratory quotient reaches 0.76. The difference between a requirement of energy of 4.53 calories when the respiratory quotient is 0.75 to 0.80 and one of 4.27 calories when the respiratory quotient is 0.95 to 0.97, is 0.26 calorie or 5.8 per cent., which is not far from the value given by Anderson and Lusk. However, that there should be a so finely graded beneficent effect upon the cost of work throughout the whole scale of increasing proportions of carbohydrate in the metabolizing mixture is information that we owe to Krogh and Lindhard.

Marsh,[1] however, notices that there was only a slight fall in the net efficiency of an individual on the 3d day of a fat diet and that it required 11 days to note the difference of 11 per cent. observed by Krogh and Lindhard.

THE RESPIRATORY QUOTIENT OF REST CONTRASTED WITH THAT OF WORK

Work by Benedict and Cathcart[2] includes an experiment on a professional bicycle rider who rode a stationary bicycle for four hours and twenty-two minutes, accomplishing 208,000 kilogrammeters of work during this period, or nearly 13 kilogrammeters per second.

[1] Marsh, M. E.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1927, **81**, 497.

[2] Benedict, F. G., and Cathcart, E. P.: "Muscular Work," Carnegie Institution of Washington, Pub. 187, 1913.

The work was the equivalent of more than a "century run," or over 100 miles (161 kilometers). The subject rode to exhaustion. When lying on a couch before the experiment the basal metabolism of this man was 1.14 calories per minute, the R. Q. was 0.85, pulse 63, and respiration 20 per minute. The *basal value for the work experiment* was ascertained by determining the heat production of the man sitting on the bicycle and revolving the wheel when it offered no resistance. The work was begun about 12 hours after food ingestion and was therefore accomplished while the man was in the *post-absorptive* state.

The following table presents the results:

METABOLISM DURING A "CENTURY RUN" ON A BICYCLE
(Subject, M. A. M.; weight = 65.9 kilograms)

Time	9 A. M.	9.45 A. M.	10.30 A. M.	11.15 A. M.	12.00 Noon	12.45 P. M.	Average
O_2 liters per minute	1.97	1.95	1.97	1.95	2.00	1.90	
R. Q	0.90	0.91	0.89	0.89	0.97	0.88	0.91
Pulse-rate	129	128	136	156	160		
Respiration rate	30	32	30	36	36		
Work done per minute (calories)	1.96	1.96	1.97	1.94	1.92	1.73	1.95
Mechanical efficiency (per cent.)	34.0	34.4	34.2	34.3	31.4	30.4	
Calories per minute	9.66	9.58	9.65	9.54	10.01	9.28	9.75
Basal value* (calories)	(3.89)	(3.89)	(3.89)	(3.89)	(3.89)		

* No load experiments without motor.

It is of great interest that the respiratory quotient should have remained at about 0.90 throughout the experiment, which indicated that the body's glycogen was being used in goodly measure throughout the whole period. A calculation shows that 368 grams of glycogen must have been consumed during the time of the ride. The average respiratory quotients of thirty-four days of experimentation with this individual present the following results:

	Rest	Work	After Work
R. Q	0.85	0.88	0.78

The lower respiratory quotient after mechanical work indicates the exhaustion of body glycogen.

The production of 600 calories per hour is probably in the neighborhood of the highest possible maximum of human physical capacity for sustained effort (see p. 460). The mechanical efficiency of 33 per cent. is the same as that previously described by the Zuntz school

for raising the body of an individual in mountain ascents. The leg muscles are, therefore, remarkably efficient machines.

The constancy of the effort hour after hour is a striking commentary on the constancy of the animal machine.

This work confirms that of Johansson,[1] that the subjective sense of strain or fatigue has no influence upon metabolism.

Benedict and Cathcart further report a considerable increase in the basal metabolism obtained lying down after severe muscular work, the stimulating influence persisting for five or six hours. For example, a man whose basal metabolism was determined as 1.15 calories per minute rode a bicycle seventy-four minutes, doing work which was the equivalent of 2.06 calories per minute. During four and a half hours of subsequent rest the basal metabolism was determined eight times, and gave values between 1.35 and 1.33 calories per minute in each instance. The rate of the pulse fell from 93 in the first observation to 75 in the last, that of the respiration from 24 to 22.

Bornstein, Griesbach, and Holm[2] report an interesting experiment upon a man riding a bicycle. There was no change in the respiratory quotient due to work, though there was a greater actual utilization of carbohydrate. The authors conclude that, since the blood sugar remains constant, it is necessary to assume a production of sugar from fat, forgetting the glycogen reservoirs of the body which can constantly replenish exhausted blood sugar.

The experiment itself is here recorded:

BICYCLE EXPERIMENT

Time	O_2 per Min.	R. Q.	From Carbohydrate per Min.	Blood Glucose
Minute	C.C.		Cals.	Per Cent.
Rest	219	0.83	0.46	
"	218	0.84	0.48	0.092
Work, 11th to 18th	571	0.83	1.12	
Work, 22d to 30th	578	0.82	1.11	0.094

As a rule it requires a little time after the beginning of severe muscular effort to reach a steady state of exchange between the oxygen absorption and carbon dioxid elimination because a quickened ventilation removes carbon dioxid from the blood. On the other

[1] Johansson, J. E.: Skan. Arch. Physiol., 1901, **11**, 273; Frumerie, K.: *Ibid.*, 1913, **30**, 409.

[2] Bornstein, A., Griesbach, W., and Holm, K.: Z. ges. exper. Med., 1924, **43**, 391.

hand, during the recovery period carbon dioxid is at first retained by the blood. To obtain a true picture of the oxidation process a "recovery period" of 10 to 15 minutes must be taken into account. One example of this has already been given (see p. 96). Another from the experiments of Soma Weiss[1] is given below:

	R. Q.	R. Q.
Forced respiration (3 and 5 min.)	1.34	0.89
Recovery period (6 to 10 min.)	0.66	0.46

Under the title, "The Maximum of Human Power and Its Fuel," Henderson and Haggard[2] present investigations made upon the Yale University crew which, having won in the United States, was winner of the Olympic championship at Paris in 1924, rowing there over a 2000 meter ($1\frac{1}{4}$ miles) course on the Seine in 5 min., 51 sec., a world's record.

In rowing there is a combined use of the muscles of the legs, arms, and back. Rowing a four-mile race at home in 22 minutes, the average energy production for each member of this crew was at the rate of 19 calories per minute or 1140 per hour. The work done per minute in the shorter race at Paris was even greater.

The authors founded their conclusions upon experiments made upon the members of the crew during periods of hard rowing upon rowing machines for periods of 3 to 5 minutes in the gymnasium. The resting metabolism was first taken. The men then worked for the stated interval and the respired air of the following 10 or 15 minutes of the recovery period was added to that of the working period to obtain the respiratory quotient. The results upon seven individual oarsmen are as follows:

R. Q. AT REST, ROWING 3 to 5 MINUTES, PLUS 10 TO 15 MINUTES REST

Rest	0.82	0.83	0.80	0.94	0.79	0.86	0.75
Work	0.92	0.85	0.82	0.85	0.78	0.77	0.73
Cals. per min.: Rest	2.13	1.65	1.42	1.44	2.10	2.68	2.4
Work	21.33	18.90	21.83	15.89	22.01	20.72	29.37

It is evident that one may conclude from the above that in trained athletes the respiratory quotients obtained during work are about the same as those found at rest. The heat production during rowing rose to tenfold that obtained from the man sitting in the rowing seat.

[1] Weiss, S.: Biochem. Z., 1920, **101**, 7. See also Liljestrand, G.: Skan. Arch. Physiol., 1918, **35**, 199.

[2] Henderson, Y., and Haggard, H. W.: Am. J. Physiol., 1925, **72**, 264.

Marsh[1] finds that when a moderate amount of work of between 8.4 to 11.2 calories is done per minute, the respiratory quotient of the material oxidized for the performance of the work depends on the character of the previous diet. The following is her table:

SUBJECT B. C. MILD OR MODERATE WORK

Diet	Excess Calories for Work Average per Minute	R. Q. of Excess Metabolism
Normal	8.4	0.95
CH	11.2	0.95
CH	8.8	1.00
Fat	11.2	0.83
Fat	8.8	0.80

The same dependence upon the quality of the diet for the source of muscular energy is also demonstrated for the dog by Rapport and Ralli.[2] The dog walked on a treadmill for 45 minutes 18 hours after the last intake of food. The diets were mixed or consisted of meat and fat or meat and carbohydrate.

EFFECT OF WALKING 45 MINUTES, AT 1.2 TO 1.6 MILES PER HOUR, UPON THE R. Q. UNDER DIFFERENT DIETARY CONDITIONS

Diet in Calories			Basal R. Q.	R. Q. of Excess Metabolism
Protein	Fat	Carbohydrate		
Per Cent.	Per Cent.	Per Cent.		
15	30	55	0.82–0.85	0.86–0.95
10	..	90	0.91	0.90
10	90	..	0.74–0.76	0.72–0.74

In the light of all this evidence the conclusion seems inevitable that the source of muscular power may be either carbohydrate or fat or both oxidizing together. That fat must first be converted into sugar before it can be used in the muscles is only a speculative hypothesis.

The very interesting work of Hill on the subject of sprint running will be dealt with in another part of the chapter.

THE INFLUENCE OF CLIMATE

Rubner[3] shows that a man of 70 kilograms weight, developing mechanical energy to the extent of 15,000 kilogrammeters per hour, produces practically the same quantity of carbon dioxid, no matter

[1] Marsh, M. E.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1927, **81**, 497.
[2] Rapport, D., and Ralli, E. P.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 964.
[3] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, p. 74.

what the temperature of his environment may be. The results of the experiment are as follows:

Temperature of the Air	Percentage Moisture in the Air	Carbon Dioxid per Hour in Grams	Water Excreted per Hour in Grams
7.4°	81	84.0	58.0
12.7°	84	78.5	70.8
16.7°	59	97.0	138.1
17.5°	87	84.5	90.4
18.8°	83	81.2	112.8
25.0°	47	78.7	230.0

This person while at rest and at a temperature of 21.1° excreted 33.6 grams of carbon dioxid and 42 grams of water.

It is clear that during work the metabolism is independent of surrounding temperature or climatic conditions. In other words, *during mechanical work the influence of the "chemical regulation" of body temperature may be eliminated* (see p. 157). The extra heat produced in doing mechanical work is utilized instead of heat which is excited reflexly through cold. These results were forecast by Voit.[1]

Generally speaking, neither clothing nor temperature affects the amount of the metabolism during exercise. They influence only the quantity of water eliminated in the perspiration, in the effort of the body to maintain its normal temperature through physical regulation. It is evident from Rubner's details of the water excretion that at a low temperature the extra heat production during mechanical exercise is lost by radiation and conduction. Rubner explains that the slight increase in the excretion of water above that lost while at rest is due to its increased evaporation through increased respiratory activity. At a higher temperature conduction and radiation become insufficient to cool the body, and a large proportion of the loss of heat takes place at the expense of the evaporation of sweat.

In hot, moist climates, however, the cooling of the body through the evaporation of moisture becomes difficult, and this is especially pronounced in the case of fat people (p. 161), who with difficulty discharge the heat produced within them. Broden and Wolpert[2] show the effect of the action of temperature and humidity on the metabolism of a fat man, weighing 101 kilograms, who executed the same amount of mechanical work under various conditions of experimentation. The work was light, being 5375 kilogrammeters per hour. The results were as follows:

[1] Voit, C.: Z. f. Biol., 1878, **14,** 152.
[2] Broden, A., and Wolpert, H.: Arch. f. Hyg., 1901, **39,** 298.

EFFECT OF WORK, TEMPERATURE, AND HUMIDITY ON THE METABOLISM OF A FAT INDIVIDUAL

Temperature	Grams per Hour			
	Dry Air		Humid Air	
	CO_2 in Grams per Hour	H_2O in Grams per Hour	CO_2 in Grams per Hour	H_2O in Grams per Hour
20°	47.8	....	46.4	
28–30°	47.3	....	48.0	
36–37°	50.3	319 + 38 gm. sweat	60.7	269 + 266 gm. sweat

This individual was the same already mentioned (p. 161), and the explanation given there is equally applicable here. In a dry climate the same amount of mechanical work may be accomplished by a fat person at both 20° and 30° without changing the metabolism. At a temperature of 37° the metabolism rises, for the cooling power of the evaporating sweat does not seem sufficient to act through the dense covering of fat. This action is intensified in moist air, where the evaporation of water is hindered. Under these latter conditions the small amount of work was accomplished only at the expense of great discomfort and profuse perspiration.

The obese, therefore, work under great disadvantage in a hot, and especially in a hot and moist, climate. The profuse perspiration explains their desire for water to drink.

INFLUENCE OF MUSCULAR WORK UPON THE BLOOD GASES

Barcroft[1] climbed a straight path to a height of 1000 feet (303 meters) in thirty minutes, a performance which involved only moderate effort. Observations of the carbon dioxid content of the alveolar air and the hydrogen ion concentration of the blood gave the following results:

	CO_2 in Alveoli Mm.	pH of Blood
Normal	40	7.29
After ascent	35	7.09

The difference in acidosis corresponds to an addition of 0.023 per cent. of lactic acid to the blood. In another subject (Roberts) who made the same ascent the amount of lactic acid necessary to reduce the alkalinity of his blood to the level actually found was estimated

[1] Barcroft, J.: "The Respiratory Function of the Blood," Cambridge, England, 1914, p. 236.

at 0.029 per cent., and the increase, as determined by analysis of the blood, amounted to 0.032 per cent. Barcroft gives the following analysis of this state of affairs: During the ascent lactic and carbonic acids, and these only, were added to the blood. On account of the increased hydrogen ion concentration, the hemoglobin at a given pressure takes up oxygen less readily than usual and the respiratory center is stimulated. The increased respirations cause the excessive carbon dioxid produced to be expired, and not only the excess but somewhat more than this; the carbonic acid pressure in the alveolar air therefore falls. Lactic acid, however, is not got rid of so quickly as the carbon dioxid, and is retained. The increase in the hydrogen ion concentration of the blood causes a readier dissociation of the oxyhemoglobin contained in the large and quickly flowing volume of blood which passes through the capillaries of the muscle. At the same time the increased ventilation of the lungs increases the oxygen tension in the alveoli, and, since the absorption of oxygen by the plasma is proportionate to the oxygen pressure, the decreased avidity of hemoglobin for oxygen caused by the increased hydrogen ion concentration is compensated for.

Barr and Himwich[1] have made important contributions to this subject. The period of work was 3 minutes upon a stationary bicycle developing in all 3500 kg.-m. of work. This large amount of suddenly performed work led to a fall in the CO_2 combining power of venous blood, a fall or a rise in the CO_2 tension, a fall in the pH, and an increase in the lactic acid present in the blood. The following table gives their results:

CHANGES IN CO_2 COMBINING CAPACITY, THE CO_2 TENSION, AND REACTION OF VENOUS BLOOD AFTER EXERCISE

Subject	Amount of Work	CO_2 Capacity at 40 Mm.			CO_2 Tension of Venous Blood			pH		
		Before	After	Dif.	Before	After	Dif.	Before	After	Dif.
	Kg.-m.	Vol. Per Cent.	Vol. Per Cent.	Vol. Per Cent.	Mm. Hg	Mm. Hg	Mm. Hg			
D. P. B.	3550	45.7	37.2	8.5	48.0	44.5	− 3.5	7.29	7.22	0.07
K. G. H.	3490	49.0	30.5	18.5	47.2	72.5	+25.3	7.33	7.03	0.30

When venous and arterial blood were withdrawn simultaneously from the arm 3 minutes after vigorous exercise with the leg muscles,

[1] Barr, D. P., Himwich, H. E., and Green, R. P.: J. Biol. Chem., 1923, **55**, 495; Barr and Himwich: *Ibid.*, pp. 525, 539; **57**, 363; Barr: *Ibid.*, **56**, 171.

the CO_2 combining power of the venous blood was always higher than that of the arterial blood, due to the fact that the resting muscles of the arm were withdrawing lactic acid from the circulation, lactic acid which had been produced in the active muscles of the leg. Three minutes after exercise lactic acid was still escaping into the blood from the tissues which had been active, and here the lactic acid content of venous blood was higher than in arterial blood. The pH of the venous and arterial bloods remained in surprisingly close agreement.

While accomplishing this amount of work the minute volume of the respiration rose from 8 to as high as 84 liters per minute, but Barr can find no constant relation between the minute volume of the respiration and the pH of arterial blood.

	Blood pH	Minute Volume of Respiration Liters
Before exercise	7.30	8
1 minute after exercise	7.16	56
3 " " "	7.15	34
15 " " "	7.23	11

Barr and Himwich find also that both the oxygen content and the oxygen capacity rise in arterial blood as the result of vigorous muscular exercise upon a bicycle ergometer. They conclude that anoxemia plays no part in the hyperpnea produced by exertion which is not carried to exhaustion.

Lundsgaard and Möller[1] have reported upon the condition of the blood after fast running up and down stairs for a minute or more. The oxygen content of venous blood drawn from the cubital vein was found to be low only during the first minute after exercise was finished. Two to 4 minutes after exercise venous blood drawn from the arm contains almost as much oxygen as arterial blood, and after 5 to 8 minutes the value returns to normal. Evidently the oxygen during the first minute is used in the "recovery phase" of muscular contraction in accord with the Hill-Meyerhof theory, and later the hyperpnea temporarily furnishes oxygen in unwonted measure.

A recent analysis of the situation is by Cordero,[2] of Erlanger's laboratory, in which it is shown that the curve of CO_2 tension in alveolar air during recovery from a short period of muscular exercise is concave downward and is roughly inverse of the published curves

[1] Lundsgaard, C., and Möller, E.: J. Biol. Chem., 1923, **55**, 477.
[2] Cordero, N.: Am. J. Physiol., 1926, **77**, 91.

of lactic acid disappearance from the blood and the disappearance of the "oxygen debt" (see p. 442).

Finally, L. J. Henderson[1] reports the following contrasts in arterial blood drawn before and after exercise. Except for the increase in the pH the results are like those of Barr and Himwich.

ARTERIAL BLOOD OF A. V. B.

	Oxygen		CO_2 Combining Power	pH	Lactate
	Capacity	Absorbed per Min.			
	Vols. Per Cent.	C.c.	Vols. Per Cent.		Millimols per Liter
Rest	21.3	250	46.5	7.34	2.1
Work	23.2	2467	40.9	7.42	8.9

The increase in lactate is stated to be much more than the equivalent decrease in bicarbonate.

The concentration of hemoglobin in the blood during mechanical work may be greater than during rest. In the case of A. V. B. mentioned above it was 8.93 millimols per liter during rest and 9.82 during work. This explains the rise in the oxygen capacity of the blood.

THE INFLUENCE OF MUSCULAR WORK ON THE BLOOD SUGAR

Although from Zuntz's work it seems proved that, in furnishing power for mechanical work, carbohydrates and fat are replaceable one for the other according to their dynamic values, there is a well-founded belief that work may be obtained in larger quantity from an individual if carbohydrates be available.

Brösamlen and Sterkel[2] made the observation that the blood sugar fell slightly from a level of 0.08 to one of 0.07 following fatiguing muscular work accomplished in the morning in the post-absorptive condition. In the diabetic a rise of blood sugar took place which the authors attributed as being due to glycogenolysis without oxidation of the sugar produced.

The sugar content of the blood has been observed[3] after a Marathon race of 25 miles (40 kilometers) and found to be subnormal. The following year moderately large quantities of carbohydrate were

[1] Bock, A. V., Dill, D. B., Hurxthal, L. M., Lawrence, J. S., Coolidge, T. C., Dailey, M. E., and Henderson, L. J.: J. Biol. Chem., 1927, **73**, 749.

[2] Brösamlen, O., and Sterkel, H.: Deut. Arch. klin. Med., 1919, **130**, 358.

[3] Gordon, B., Kohn, L. A., Levine, S. A., Matton, M., Schriver, W. de M., Whiting, W. B.: J. Am. Med. Assn., 1925, **85**, 508.

administered before the race, and during the race candies and tea containing sucrose were ingested. At the end of the race the blood sugar was normal, and the physical condition and running time were better than the year before. The authors conclude that perhaps exhaustion, weakness, and shock due to prolonged exercise, are attributable to hypoglycemia, which is cured by adequate and timely ingestion of carbohydrate.

Schumburg[1] finds that ingestion of carbohydrates enables a fatigued muscle to contract more powerfully. Hellsten[2] states that in doing mechanical work in the morning before breakfast, an improved capacity occurs thirty to forty minutes after ingesting sugar.

The ready exhaustion of diabetics who cannot burn glucose confirms this observation.

Lee and Harrold[3] have found evidences of great fatigue in the excised muscles of a cat from which the readily combustible sugar had been removed by rendering the cat diabetic with phlorhizin. Another cat similarly treated, the body of which, however, had been flooded with sugar by ingestion before the animal was killed, showed a much larger capacity for muscular contraction.

The writer[4] while injecting phloretin solutions into the jugular vein of fasting rabbits, diabetic through phlorhizin, noticed that seven out of eight rabbits had convulsions, while normal rabbits were not so affected. Four died and three lost motor control of the muscles of their limbs. In these three there was an increased glucose elimination in the urine on account of the passage of the glycogen content of the organs into the blood, which glycogen would normally be immediately available for muscular activity (p. 107). The animals which survived the convulsions regained control of their muscles in two to four hours. Since the discovery of insulin it is known that the convulsions are due to hypoglycemia, and may be preceded by nervousness and prostration.

Parker and Finley[5] have shown that in certain types of nervous disorders, benefit may be derived from the ingestion of glucose.

[1] Schumburg, H.: Arch f. Physiol., 1896, p. 537.
[2] Hellsten, A. F.: Skan. Arch. Physiol., 1904, **16**, 139.
[3] Lee, F. S., and Harrold, C. C.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1900–01, **4**, p. ix.
[4] Lusk, G.: Z. f. Biol., 1898, **36**, 109.
[5] Parker, J. T., and Finley, C. S.: Proc. Soc. Exper. Biol. and Med., 1923–24, **21**, 517.

In many English homes it is customary to take tea before arising in the morning and tea is always and everywhere served in England in the afternoon. Tea taken with sucrose and a bit of bread or toast maintains the blood sugar at a desirable level.

Schumburg[1] finds that coffee and tea have no recuperative power over the muscles of a fatigued organism except when taken with other foods, and that the stimulating action of alcohol is only temporary. Hellsten,[2] exercising before breakfast, finds that the effect of taking tea is almost negligible, and that the effect of alcohol is at first to increase the muscle power, but that after twelve to forty minutes there is a decrease in power which lasts for two hours. No such depression occurs after taking sugar.

Simonson,[3] however, states that administration of 3 to 6 c.c. of alcohol in all experiments in which mechanical work was done reduced by 8 to 15 per cent. the number of calories required to do severe work. The rapidity of recuperation after fatigue is promoted. Simonson suggests that alcohol acts to improve the recovery process in muscle, or perhaps that it acts on the contractility of muscle so that the amount of work per gram of lactic acid produced is increased. The interpretations follow the lines of the Hill-Meyerhof theory.

The factor of hypoglycemia may very probably be invoked to explain *the reaction of undernourished men to physical fatigue*. The following very striking picture is given by Jansen.[4]

The official ration in Munich in March, 1917, was food containing 1600 calories and 9.7 gm. of nitrogen. The ration was given to several men who were occupied as hospital internes. The men had all lost weight since the beginning of the war. The average weight of the subjects was 62 kg. While taking the diet each person lost about 2 gm. nitrogen daily. The addition of 500 calories in the form of sucrose to the diet prevented the loss of body nitrogen and of body weight, indicating that the difficulty lay in a deficiency of calories in the diet.

In the usual form of experimentation upon people taking the official ration the subjects were inactive or were doing only light work. But in this series the metabolism of men who accomplished heavy work while partaking of an insufficient diet was investigated.

[1] Schumburg, H.: Arch. f. Physiol., 1896, p. 537.
[2] Hellsten, A. F.: Skan. Arch. Physiol., 1904, **16**, 139.
[3] Simonson, E.: Arch. exper. Path. u. Pharm., 1927, **120**, 259.
[4] Jansen, W. H.: Deut. Arch. klin. Med., 1917–18, **124**, 1.

Three subjects abstained from muscular exertion during 3 days and then walked together for 3 days over level ground in part during a driving snow storm, while underfoot there was mud and melting snow, making the walking exceptionally difficult and wearisome. The daily distances accomplished were 18, 20, and 25 km. (11, 12.4, and 16 miles). The labor of such walks would not have been great under normal dietary conditions, yet the subjects returned home each day over fatigued and exhausted. One of them on his return fell into a state of prostration through weakness. The skin was pallid, respiration shallow and quickened, pulse small and slow, temperature subnormal, profuse sweating from the whole body surface; there was no aceton in the urine. Another of the subjects gave indications of similar symptoms on the second day. Apathy and psychic depression were present in all three men during the evenings of these days of exertion. The experiments present two different findings as far as the protein metabolism is concerned. In one person the protein metabolism was not increased as the result of the muscular work. In the other two persons the nitrogen deficit increased about 1 gm. daily above the increase which accompanied the low calorie diet. This corresponds to an increase of about 10 per cent. in the total protein metabolism of the period. The average weight of the men fell to 57 kg. Two of the men were subjected to respiration experiments twelve hours after the second and third days of walking. These experiments had to be carried out at so late an interval because the persons concerned were too exhausted on their return from their walks to be satisfactory subjects for experimentation. Both experiments yielded surprising results, both as regards the duration of the after-effects of the exercise and the height of the metabolism. In this series of experiments high respiratory quotients were found twelve hours after the walk was finished. Although the height of the respiratory quotients fell during the progress of the experiment the average of all the determinations was about unity. The explanation of this high value lies in the irritable condition of the subject. The subjects who had formerly yielded themselves freely to this form of experimentation no longer had either the will power or the physical energy requisite for accomplishing an exact experiment and fell into a state of excitement, which was manifested by the increased respiratory movements. The ventilation of the lungs was abnormally increased.

The experiments were done in the laboratory of the second medical clinic in Munich during the World War under the direction of Friedrich von Müller. They were used as a convincing argument against the rationing of bread to the British population during the war.

The basal metabolism of one of the men the day after exercise was 2160 calories for 24 hours, in contrast with 1440 calories before during the period of no muscular work.

Ilzhöfer[1] interprets these findings as due to the increased susceptibility of the respiratory center and other nerve centers toward hydrogen ions. It may, however, have been due to hypoglycemia, whatever be the cause of the symptoms following in the train of this condition.

It seems evident that *muscular effort in the undernourished human being is accomplished with great inefficiency, in contrast with the easy performance of work by the fasting dog.*

In Great Britain during the war many men of sedentary occupation, who submitted to the "voluntary ration" of bread suggested by the Government, underwent hardship accompanied by nervous irritability which Carl Voit first noticed was a result of undernutrition.

VARIOUS CALCULATIONS SHOWING THE REQUIREMENT OF ENERGY FOR MUSCULAR WORK

Johansson and Koraen[2] have caused a man to raise a weight of 21.7 kilograms $\frac{1}{2}$ meter high, each movement lasting one second, and there being in different experiments 300, 600, 720, and 900 movements per hour. In the trained individual the quantity of increase in the carbon dioxid expired was exactly proportional to the number of the movements in the unit of time. The experiments were performed when food was absent from the intestines.

It has already been shown (see p. 412) that 25 per cent. of the total energy of the increase above the resting metabolism as caused by work is converted into mechanical energy by a person turning the wheel of an ergostat with his arms.

Katzenstein[3] has shown a still more economical utilization of the fuel when the work accomplished is climbing, about 35 per cent. of the total increase in metabolism being then converted into mechani-

[1] Ilzhöfer, H.: Arch. f. Hyg., 1919, **88**, 285, 332.
[2] Johansson, J. E., and Koraen, G.: Skan. Arch. Physiol. 1903, **14**, 60.
[3] Katzenstein, G.: Pflüger's Arch. gesam. Physiol., 1891, **49**, 379.

cal effect. Walking, the commonest muscular exercise, is accomplished with the greatest mechanical efficiency.

A great many interesting details have been worked out in Zuntz's laboratory by his pupils. The following epitome of long investigations shows the comparative energy equivalents necessary for dog, horse, and man to move 1 kilogram of body weight 1 meter with a given rapidity along a horizontal plane or to lift 1 kilogram of body weight 1 meter high.[1] The experiments were made by placing the individual on a moving platform, the speed and incline of which could be varied.

A study of the table on p. 431 will show that it requires much less energy for a horse to move 1 kilogram of his weight 1 meter horizontally than for a dog to do the same at the same velocity. It also appears that a man of small weight requires more energy to a unit of substance than does a man of large size. This rule has been confirmed in dogs by Slowtzoff,[2] who shows that energy amounting to 0.529 kilogrammeter is required for 1 meter horizontal motion by a dog weighing 37 kilograms, and 1.138 kilogrammeters by a dog weighing 5.5 kilograms. Slowtzoff does not find that this variation is proportional to the skin area of the animal.

The table also shows that there is little variation in the dog, horse, and man in the amount of energy necessary to raise 1 kilogram of body substance 1 meter high.

It is possible to calculate the food ration for a march if the figures given in the table be employed. If it be assumed that a man weighing 70 kilograms travels 74.4 meters a minute, he will accomplish 4.46 kilometers or 2.8 miles per hour. If it requires the energy equivalent of 0.217 kilogrammeter to move 1 kilogram of his weight 1 meter, it will require 67,747 kilogrammeters ($0.217 \times 70 \times 4460$) to move him 4.46 kilometers—67,747 kilogrammeters being equivalent to 159.205 calories. This is the equivalent of 17.1 grams of fat, which may be added to the maintenance resting dietary requirement to supply the energy necessary for an hour's quiet walk on a level road. If the road be inclined so that the man raises himself 500 meters during the hour's walk, the metabolism will be still further increased. The work of ascent will be his weight multiplied by the height of his climb, or 35,000 kilogrammeters.

[1] Frentzel, J., and Reach, F.: Pflüger's Arch. gesam. Physiol., 1901, **83**, 494.
[2] Slowtzoff, B.: *Ibid.*, 1903, **95**, 190.

ENERGY REQUIREMENTS OF DIFFERENT ANIMALS IN PERFORMANCE OF THE SAME AMOUNT OF MECHANICAL WORK

Animal	Weight Kg.	Energy Requirement in Kilogrammeters		Velocity in Meters per Minute of Horizontal Movement	Incline of Road in Per Cent. during Climbing Experiment
		For Moving Horizontally 1 Kg. 1 Meter	For Raising 1 Kg. 1 Meter High		
Dog	26.9	0.495	2.954	78.57	17.2
Dog	26.9	0.501	3.259		
Horse	456.8	0.137	2.912	78.57	10.3
Man	55.5	0.334	2.857	74.48	9.6–13.3
	72.9	0.217	3.190	71.32	6.5
	67.9	0.211	3.140	71.46	
	80.0	0.288	3.563	51.23	30.7–62
	88.2	0.263	3.555	42.34	
	72.6	0.284	2.913	62.04	
	81.1	0.231	2.921	60.90	23–30.5
Man. F.	80.0	0.244	2.729	56.54	
Normal locomotion.. F.	86.5	0.219	2.746	66.94	23.3
Slow locomotion..... R.	86.5	0.233		35.92	
Normal..... R.	65.8	0.230	2.846	63.95	
Slow.....	65.8	0.251		34.58	

The expenditure of energy by the body in order to accomplish this work is threefold the work done, or 105,000 kilogrammeters, which equals 246.75 calories, or 26.5 grams of fat. The hour's walk in this case would require the production of an energy equivalent, above the resting metabolism, amounting to that contained in 43.6 grams of fat—that is, 17.1 grams for a forward locomotion of 4.46 kilometers and 26.5 grams to lift the body to an altitude of 500 meters.

In the last-mentioned table it is seen that there is an increase in the metabolism for a unit of horizontal motion when the progress of the individual is very slow. This is explained by the fact that speed of progress was half the normal, was unusual, and dilatory.

Later work has confirmed the results above enumerated. Thus, Brezina and Reichel[1] find that a man walking on a horizontal plane at a rate not exceeding 80 meters in one minute (3 miles per hour), a rate which they denote as the *maximal economic velocity*, requires 0.5 calorie of energy (= 0.213 kilogrammeter of work) to move 1 kilogram of weight 1 meter, and this rule also applies to weights carried up to about 20 kilograms. This load is about that carried

[1] Brezina, E., and Reichel, H.: Biochem. Z., 1914, **63**, 170.

by a soldier. With weights heavier than this there is a slight increase in the quantity of energy required when the individual labors within the limits of the maximal economic velocity. When, however, this velocity is exceeded the expenditure of energy for more rapid walking increases rapidly, and with especial sharpness when heavy loads are carried. A part of the figures is given in the following table:

THE INFLUENCE OF VELOCITY AND OF LOAD IN HORIZONTAL WALKING UPON THE AMOUNT OF ENERGY IN GRAM-CALORIES NECESSARY TO MOVE 1 KG. OF WEIGHT THROUGH 1 METER OF DISTANCE

Distance in Meters per Minute	Miles per Hour	Load Equals 3 Kg.	Load Equals 14 Kg.	Load Equals 24 Kg.	Load Equals 36 Kg.	Load Equals 46 Kg.	Load Equals 56 Kg.
44.7– 49.7	1.8	0.48	0.48	0.57	0.59	0.58	0.59
68.9– 73.3	2.7	0.60	0.47	0.52	0.53	0.56	0.59
89.9– 92 0	3.4	0.57	0.62	0.59	0.64	0.81	0.77
111.4–118.1	4.3	0.77	0.93	0.91	0.91		
141.0	5.3	0.93					

Benedict and Murschhauser[1] have arrived at essentially the same results as those given above as regards the energy requirement involved in horizontal walking, and they further note that running at the rate of about 5.3 miles per hour is accomplished more economically than walking at the same rate. Their results may be summarized as follows:

	Distance in Meters per Minute	Gram-calories for Horizontal Kilogram 1 Meter
Walking	71.5	0.493
	106.3	0.585
	144.1	0.932
Running	147.5	0.806

The total heat produced when walking at the higher speed was about 600 calories per hour, or about that of the same individual (M. A. M.) when he rode a bicycle, as already described (p. 417). At the lower speed it was found that the process of walking involved a total lifting of the body weight from the ground, amounting approximately to a height of 4 meters per minute. The energy necessary to do this would account for 25 per cent. of the total energy utilized in the muscular complex thrown into action for the purpose of forward progression.

The generalization of Brezina and Reichel is that within the limit of economic maximal velocity the energy requirement of the organ-

[1] Benedict, F. G., and Murschhauser, H.: "Energy Transformations During Horizontal Walking," Carnegie Institution of Washington, Pub. 231, 1915.

ism approximates a constant minimum value, which is 0.5 gram-calorie for the forward movement of 1 kilogram of weight 1 meter horizontally. With each meter of velocity above 80 meters per minute the requirement of energy increases 1 per cent. of the initial minimal value. When medium loads (20 kg.) are carried the metabolism increases 2 per cent., and with heavy loads 3 per cent., of the minimal value, per each added meter of velocity above 80 meters per minute.

The rule is that the metabolism increases with speed in horses (1.03 per cent. per meter increase above 78 meters per minute), but this is not seen in dogs.[1]

Brezina and Reichel[2] continued their researches by determining the effect of the gradient of the pathway upon the metabolism of man when walking and carrying different loads. It was found that the maximal work of lifting the body with its load was accomplished at a minimal expenditure of energy when the incline was 20 per cent. and the weight of the load 19 kilograms. However, when walking on inclines with gradients of 10 or 40 per cent., the energy figures were only slightly above the minimal values and the load also made no essential difference. The authors found that to raise 1 kilogram of body substance plus the load carried to a height of 1 meter, required between 9 and 10 calories of energy of metabolism. This represents the conversion of about 25 per cent. of the energy of metabolism into mechanical work. Weights between 3 and 56 kilograms were raised at expenditures of energy directly proportional to the work accomplished.

Atzler and Herbst[3] have studied the factors (*a*) number of steps per minute, (*b*) length of stride, and (*c*) speed per minute in meters and find that for a man weighing 70 kg. optimal results are obtainable when 87.5 steps are taken per minute with a length of stride of 58.7 cm. (about 2 feet) and a speed of 51.4 meters per minute (2 miles per hour). The subject walking upon a moving platform could move his body under these conditions at a minimal expenditure of 0.5 calorie for each kilogram of body weight moved forward one meter. This is also Durig's value.

The cost of the mileage traveled when 50 steps of 2 feet each in length at a rate of 0.86 mile per hour are taken is the same as when

[1] Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1903, **95**, 192.
[2] Brezina, E., and Reichel, H.: Biochem. Z., 1914, **65**, 35.
[3] Atzler, E., and Herbst, R.: Pflüger's Arch. gesam. Physiol., 1927, **215**, 291.

150 steps are taken per minute with the same length of step and 2.55 miles are covered. Both procedures are very uneconomical. Also the cost per mile traveled is 20 per cent. heavier when the steps are 3 feet each in length, their number 50 per minute, and the distance covered 1.7 miles per hour, than when the step remains at 3 feet while their number is trebled (150) and the distance also is trebled.

These factors stand out in the following table:

Number of Steps per Min.	Length of Stride, Cm.	Speed		Calories
		Meters per Min.	Miles per Hr.	Per Meter and Kg.
50	46	23	0.86	0.698
50	90	45	1.6	0.980
75	45	34	1.2	0.530
75	90	67	2.4	0.717
100	45	45	1.6	0.530
100	61	61	2.2	0.516
100	90	90	3.24	0.646
150	45	68	2.45	0.738
150	90	135	4.86	0.822

Smith and Doolittle[1] conclude that there is no difference in the increment of energy used for walking by women as contrasted with that used by men. They present these results:

AVERAGE ENERGY PER KILOGRAMMETER IN GRAM CALORIES

Women		Men	
Speed in Meters per Min.	Gm.-cals. for 1 Kg. 1 Meter	Speed in Meters per Min.	Gm.-cals. for 1 Kg. 1 Meter
30	0.528	37	0.449
60	0.486	65	0.463
90	0.553	91	0.553

They also report that the menstrual period has no influence on the standing metabolism of women.

Katzenstein[2] finds that the metabolism during the descent of a mountain is less by 10 per cent. than the increase caused by walking on a level surface. The muscles which act to inhibit a too rapid descent are not required to be so active as those which give forward impetus to the body on a level road.

[1] Smith, H. M., and Doolittle, D. B.: J. Biol. Chem., 1925, **65**, 665.
[2] Katzenstein, G.: *Loc. cit.*, p. 376.

This idea has been still further investigated by mountaineers,[1] who compared the actual heat production with the energy of metabolism during one minute for horizontal motion and for ascent and descent of a mountain path which had a 25 per cent. incline. The results were as follows:

	Ascent, 28.8 Meters	Horizontal, 100 Meters	Descent, 76 Meters
Calories of energy of metabolism	69.3	67.8	40.8
Calories of heat liberated	46.9	67.8	85.5

The smallest liberation of heat occurred during the ascent of the mountain at the time when the energy of metabolism was being converted into energy of position.

The largest heat production occurred during the descent of the mountain. The metabolism was the least, but energy of position was converted into heat through the vibration of the body at each footfall.

Zuntz and Schumburg[2] find an increase in the metabolism of a marching soldier if the knapsack be badly placed, or if the body be sore and weary.

Lavonius[3] finds the maximum amount of work attainable by a trained wrestler of great reputation to be the equivalent of 30 kilogrammeters per second.

Details of the effect of position upon the metabolism of individuals have been repeatedly published by Benedict and his pupils. Perhaps the most interesting of these studies may be taken from the work of Benedict and Murschhauser[4] upon the basal metabolism of the professional bicycle rider, M. A. M. The results may thus be summarized:

Position	Calories per Minute	Pulse-rate
Lying (basal metabolism)	1.14	
Sitting	1.19	61
Standing, relaxed	1.25	80
Standing, hand on staff	1.26	80
Standing, leaning on support	1.18	78
Standing, "attention"	1.30	73
Standing, swinging arms*	3.13	

* As in rapid walking.

[1] Zuntz, N., Loewy, A., Müller, F., and Caspari, W.: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," Deut. Verlagshaus Bong u. Comp., 1906.

[2] Zuntz, N., and Schumburg, H.: "Studien zu einer Physiologie des Marsches," Berlin, 1901.

[3] Lavonius, H.: Skan. Arch. f. Physiol., 1905, **17**, 196.

[4] Benedict, F. G., and Murschhauser, H.: *Loc. cit.*

A subject of very great interest in the result of training. It is well known that if a cobbler, for example, be removed from his trade and be compelled to climb a mountain, he will at first be of little use as compared with a Swiss guide. But after continued practice the blood-vessels dilate at once in response to the needs of the muscles and the heart expends less energy; unnecessary motions with the arms and legs are diminished in number; the strain for the accomplishment of a given piece of work diminishes; the thorax enlarges to promote readier respiration; the man becomes "trained," and there is a lessened metabolism for the fulfilment of a definite amount of work.

The experimental measurements of the efficacy of the working organism as described above were made on well-trained men, a difference on account of training having been early recognized by Zuntz.

Bürgi[1] made some investigations upon an individual before and after training for mountain climbing. The ascents were made at different altitudes on the roadbed of mountain railways, and the carbon dioxid elimination was measured. The results are shown in the following table:

EFFECT OF TRAINING ON METABOLISM

Place	Altitude in Meters	Incline of Road in Per Cent.	CO_2 Excretion per Kg.-m. of Work	
			Untrained	Trained
Brienz	620	17.29	2.430	2.103
Gornergrat	2987	19.3	2.711	2.268
Brienz	690	19.0	2.251	2.063
Gornergrat	3021	19.3	2.445	2.117

It is evident from this that a trained mountaineer accomplishes his work at the expense of less metabolism than does the untrained. Also that at a moderately high altitude (3000 meters = 522 mm. of mercury, barometric pressure) the trained organism is as efficient for mechanical work as at the sea-level, whereas the untrained man requires a much greater metabolism to accomplish a unit of work at the higher altitude than at the lower.

Another fact of importance is that the effect of training especially affects the muscles involved in the particular movement, and not those which do not contract. Thus Zuntz[2] found that a dog trained

[1] Bürgi, E.: Arch. f. Physiol., 1900, p 509.
[2] Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1903, **95**, 200.

for horizontal motion on a level street required 1179 small calories to move 1 kilogram body weight 1000 meters and 7.668 small calories to raise 1 kilogram body weight 1 meter high. The dog was then gradually trained to ascend an incline. After two years he required only 5.868 small calories to lift 1 kilogram 1 meter, but he required 1343 small calories per kilogram for horizontal locomotion through 1000 meters. Therefore the specifically trained muscles work more economically than those which are at the time but little used.

A man trained for mountaineering will often find himself uncomfortable when walking on a level road. The mountaineer will not find the bicycle an easy means of locomotion,[1] nor will the bicylist unscathed essay the mountain.

A benefit derived from riding a horse is the shaking of the internal organs, which is also achieved by descending a steep pathway. This may be beneficial to the life processes in such a comparatively immobile organ as the liver for example. It also appears to promote a freer evacuation of the bowels.

In swimming there is considerable respiration gymnastics.[2] The water pressure upon the thorax is the equivalent of the weight of an 8-kilogram sand-bag, which the swimmer seeks to counterbalance by increasing the pressure in his lungs through puffing with his lips. By turning over on the back the swimmer removes this respiratory influence. Cold water stimulates metabolism (p. 157), but the effect of the salt in ordinary sea water is certainly negligible.

Experiments by Liljestrand and Stenström[3] show that a man weighing 90 kg. requires 1.53 gram calories to move 1 kg. of body weight 1 meter through the water when the speed is 20 meters per minute and 2.64 gm. cal. when the speed rises to 50 meters per minute or 1.86 miles per hour. This is five times the energy necessary to walk at the same rate. To swim at this rate for an hour requires 554 kilo-calories for a man weighing 70 kg. To this must be added 70 calories for the basal metabolism making 624 calories in all. To swim the English channel, 20 miles in 15 hr., must be an arduous undertaking.

There can be little doubt that exercise, especially in the open air, strengthens the organism and therefore tends to prolong life. Some-

[1] Concerning energy expended in bicycle riding see Berg, W., du Bois-Reymond, R., and Zuntz, L.: Arch. f. Physiol., Suppl., 1904, p. 20.

[2] du Bois-Reymond, R.: *Ibid*, 1905, p. 253.

[3] Liljestrand, G., and Stenström, N.: Skan. Arch. Physiol., 1920, **39**, 1.

times muscular exercise is mistakenly considered as favoring intellectual activity. Yet college presidents are not selected from the ranks of prize-fighters.

THE HILL-MEYERHOF THEORY OF THE ENERGY PRODUCTION IN MUSCULAR CONTRACTION

The pioneers were Fletcher and Hopkins, who noted an accumulation of lactic acid in a muscle working in a hydrogen atmosphere, which lactic acid disappeared when oxygen was admitted[1] (see p. 577).

A. V. Hill, physicist, mathematician, and physiologist of the renowned Cambridge school, using instruments of great delicacy, applied thermo-electric measurements for the determination of the thermal changes in contracting frog's muscle.[2] A single twitch of the frog's sartorius at 20° C. is accompanied by an increase in temperature of not more than 0.003° C. If the muscle was stimulated in nitrogen gas a certain amount of "initial heat" was formed, followed on relaxation by the production of a quantity of heat equal to 25 per cent. of the heat produced during stimulation. When the whole process took place in oxygen the quantity of heat produced during the "recovery" phase was 150 per cent. of that of the initial heat. It was therefore evident that if the heat production during anaerobic contraction were 1, the "delayed" heat production which ensued after the contraction would be 1 also. Both factors were of the same magnitude.

Hill,[3] in his Croonian Lecture, writes,

"It was possible—indeed, it was long supposed—that in muscle this oxygen was used during the contraction itself in some kind of explosive chemical change which induced the motion. This view is certainly wrong . . . Activity can occur in the complete absence of oxygen. Oxidation is indeed necessary, but only subsequent to activity, and in order to restore the muscle to its previous state, to provide the energy necessary to reverse the initial chemical breakdown."

In 1914 Hill[4] calculated that all the heat which was evolved in the appearance of lactic acid during the anaerobic contraction of the

[1] For the older literature consult von Kries, J.: Pflüger's Arch. gesam. Physiol., 1921, **190**, 66.
[2] Hill, A. V.: "Muscular Activity," Baltimore, 1926.
[3] Hill, A. V.: Proc. Roy. Soc. (London), 1926, B, **100**, 87.
[4] Hill, A. V.: Proc. Physiol. Soc., J. Physiol., 1914, **48**, x.

muscle and in the disappearance of lactic acid during the recovery phase amounted to only one-fourth of that which would have been liberated had all the lactic acid produced in the intermediary reaction been oxidized.

In 1919 Meyerhof[1] stated that the respiratory quotient of active frog muscle was 1.02, which further supported the idea that lactic acid was oxidized during the recovery period.

In 1920 Meyerhof[2] noticed that 75 per cent. of the lactic acid produced during anaerobic contraction was returned to the form of glycogen and that the other quarter of lactic acid or its carbohydrate equivalent was oxidized with the liberation of energy, a part of which appeared as heat and the rest of which was absorbed in the endothermic process of returning lactic acid to the form of glycogen. The heat produced was sufficient to account for the thermal changes observed by Hill.

One of Meyerhof's experiments upon the oxidative recovery of a fatigued muscle may thus be given:

	Per Gm. Muscle in Mg.		
	Fatigue	Recovery	Difference
Glycogen (as glucose)	3.37	4.75	+1.38
Other carbohydrate	2.01	1.66	−0.35
Sum of both	5.38	6.41	+1.03
Lactic acid	2.56	0.44	−2.12

He[3] has lately stated that as a general average the "oxidation quotient" of lactic acid or

$$\frac{\text{Lactic acid which disappears}}{\text{Lactic acid oxidized}}$$

is 4.7.

The evidence is therefore at hand for the following sequence of events, as given by Hill, describing the process of anaerobic contraction:

1. Glycogen disappears.
2. Lactic acid appears in equivalent amount.
3. Preformed CO_2 is driven off.

[1] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1919, **175**, 88; consult also Meyerhof's monograph "Chemical Dynamics of Life Phaenomena," Philadelphia and London, 1924.

[2] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1920, **182**, 232; **185**, 11.

[3] Meyerhof, O.: Klin. Wochenschr., 1927, **6**, 1219.

4. Heat is produced which is proportional to the amount of lactic acid formed.

5. The hydrogen ion concentration rises.

The anaerobic contraction is therefore due to the formation of sodium lactate from glycogen.

In the *recovery* or *aerobic* phase the picture is as follows:

1. One-fifth of the lactic acid is oxidized.

2. Four-fifths of the lactic acid is restored to its precursors.

The energy relations in these transformations are thus given by Hill, who utilizes Meyerhof's value for the neutralization of alkaline protein by lactic acid, as follows:

Dissolved glycogen hydrate $(C_6H_{12}O_6)_n$ 1 gm. 3,836 cals.[1]	=	Lactic acid $C_3H_6O_3$ 1 gm. 3,601 cals.	=	Energy 235 cals.
Lactic acid + K-protein				135 "
Total heat of the anaerobic initial state				370 "

The whole process works out as follows:

"Initial heat" from 1 gm. lactic acid	370 cals.
"Delayed heat" in oxidative recovery	370 "
Total heat evolved	740 "
$\frac{1}{5.2}$ gm. lactic acid oxidized	740 "

Hence, one in every 5.2 molecules of lactic acid is oxidized in order to liberate 370 cals. of delayed heat and in order to return endothermically lactic acid to glycogen.

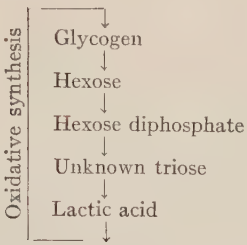
The oxidation of a portion of the lactic acid is said to maintain the circuit glycogen $\rightleftarrows$ lactic acid in the interest of muscular activity.

Embden[2] has criticised this work and finds that much lactic acid arises after the cessation of muscle stimulation. Meyerhof[3] replies that the secondary accumulation of lactic acid in the muscle in Embden's experiments is due to contracture, and if the muscle is stimulated through its nerve and not directly the phenomenon is not observed.

Further refinements of detail may be read in papers by Meyerhof[4] and by Furusawa and Hartree[5] in which the anaerobic heat per gram of lactic acid is given as 390 calories.

[1] Slater, W. K.: Biochem. J., 1924, **18,** 621.
[2] Embden, G., Lehnartz, E., and Hentschel, H.: Z. physiol. Chem., 1927, **165,** 255.
[3] Meyerhof, O.: Klin. Wochenschr., 1927, **6,** 1219.
[4] Meyerhof, O.: Pflüger's Arch. gesam. Physiol., 1924, **204,** 295.
[5] Furusawa, K., and Hartree, W.: J. Physiol., 1926–27, **62,** 203.

The possibility of a rotation like the following schema has already been discussed in another chapter:



An isolated observation of Macleod[1] in 1899 showed that 100 gm. dried muscle contained 376 mg. inorganic phosphorus, but that if the muscle had been previously fatigued 444 mg. were present. Embden and Grafe[2] were the first to show that muscular work increased the output of inorganic phosphate in the urine and associated this phenomenon with the breakdown of lactacidogen (see p. 334).

Embden's Viewpoint.—Embden[3] believes that the difference between the lactic acid content of the muscle contracting in hydrogen and that of the muscle contracting in oxygen is not due to the fact that lactic acid disappears from the muscle when it is supplied with oxygen, but rather that during the activity of the muscle in a hydrogen atmosphere more lactic acid is actually formed than under conditions when oxidation is possible. In several of his experiments he states that Meyerhof's "oxidation quotient" is over 10, indicating that for each part of lactic acid oxidized 9 must have been put back into carbohydrate. He arrives at the conclusion that the fundamental conception of the Hill-Meyerhof theory, according to which the whole of the free energy liberated at the moment of contraction is derived from the exothermic transformation of carbohydrate into lactic acid and the accompanying neutralization process, is no longer tenable.

Experiments in Man.—Hill and his pupils have developed his theory of muscular contraction in a very fascinating manner in their investigation of what happens in sprint running. In the trained athlete this form of running may be developed into an art of extreme

[1] Macleod, J. J. R.: Z. physiol. Chem., 1899, **28**, 535.
[2] Embden, G., and Grafe, E.: *Ibid.*, 1921, **113**, 108.
[3] Embden, G., Lehnartz, E., and Hentschel, H.: *Ibid.*, 1927, **165**, 255.

precision. Thus Furusawa, Hill, and Parkinson[1] made four different observations on a sprint runner who ran 60 yards in 7.43, 7.45, 7.47, and 7.37 seconds' time on the same afternoon. The first yard was run in 0.54, 0.50, 0.49, and 0.54 seconds during the different trials. The starting signal was the word "Go" and the subject then ran the following distances in the following average times:

Distance, yards..	1	3	6	10	15	20	30	40	50	60
Time, seconds....	0.52	0.94	1.43	1.97	2.59	3.15	4.23	5.29	6.38	7.43

In these four experiments the average difference between the mean and the observed time for any distance is only 0.014 second. The man attained almost maximal power after running 10 yards in 2 seconds, and subsequent 10 yard distances were traversed respectively in 1.18, 1.08, 1.06, 1.09, and 1.05 seconds. Here one sees the constancy of dynamic power of the human machine.

Sargent,[2] in Hill's laboratory, caused a man to run at various speeds over a course of 120 yards with a 20 yard "pull up." At the beginning of the race the man held his breath and at the end respired into a face mask attached to a respiration apparatus. The resting oxygen intake was 0.255 liter per minute. The following results were obtained at different rates of speed:

Speed Yd. per Sec.	O_2 for 120 Yd. Liters	O_2 per Min. Liters
5.56	1.83	5.1
6.45	2.71	8.8
7.70	3.85	14.8
8.40	4.33	18.2
9.23	7.36	34.0

In the last experiment 120 yds. were run in 13 seconds by this highly developed athlete. In the running he developed an "oxygen debt" of 7.36 liters, which was measured by the respiration apparatus. This extra oxygen intake due to work, if used to oxidize carbohydrate, would produce 37.2 calories. In terms of Hill's theory 50 gm. of lactic acid would be formed in 13 seconds or at the rate of 4 gm. per second; 10 gm. of these would then be oxidized in payment of the oxygen debt, and the other 40 gm. would be returned to glycogen once more. If the man weighing 63 kg. had 7 per cent. of blood, this blood would have weighed 4.41 kg. If the blood were all arterial and contained 20 volumes per cent. of oxygen, only 0.88 liter of oxygen would have been in the body available for the work to be done.

[1] Furusawa, K., Hill, A. V., and Parkinson, J. L.: Proc. Roy. Soc. (London), 1927, B, **102,** 29, 43.

[2] Sargent, R. M.: *Ibid.*, 1926, B, **100,** 10.

According to Hill the initial anaerobic heat obtained from the hydrolytic cleavage of glycogen into lactic acid is the fuel supply for this great effort, and the delayed heat is derived from subsequent oxidative processes, whereby the oxygen debt is paid.

It is a beautiful and satisfying theory and one may wish it well at the hands of time.

It is stated by Furusawa, Hill, Long, and Lupton[1] that "in very severe exercise the rate of lactic acid formation in a man of 51 kg., as measured by the oxygen requirement of the exercise, attained a value of 2.7 gm. per sec. In such exercise a concentration of 0.3 per cent. of lactic acid in the active muscles would be attained in just over 20 sec. and the lactic acid maximum within half a minute. This is in keeping with what is known about the limiting duration of the maximal muscular effort in athletes."

The work of Barr (see p. 424) showing that lactic acid produced in the active muscles of the legs may pass into the blood stream and be removed by another group of resting muscles, such as those of the arms, has been confirmed by Furusawa.[2] Both the muscles and the liver remove lactic acid from the blood stream and convert it into glycogen. There may be a type of exhaustion due to the complete using up of the lactic acid precursor when the fatigue product, lactic acid, is thus distributed to other organs, themselves at rest (Furusawa).

After hard exercise lactic acid rises not only in the blood but also, at a threshold value of 30 to 40 mg. per liter of blood, it makes its appearance in the urine. Thus a man climbing a treadmill without a load showed no lactic acid in the urine, but climbing and carrying a load of 20 kg. for 3 minutes brought detectable quantities of lactic acid into the urine.[3] Following 2 or 3 minutes of strenuous exercise the urine of the second 10 minute interval may contain from 86 to 630 mg. lactic acid.[4]

Lindhard[5] finds that static muscle work produced by torsion, that is by twisting the hanging arms of a subject for 60 seconds, resulted in fatigue which lasted 1 hour. During rest there were 222 c.c. of oxygen taken per minute, during muscular contraction 258 c.c.,

[1] Furusawa, K., Hill, A. V., Long, C. N. H., and Lupton, H.: Proc. Roy. Soc. (London), 1924, B, **97**, 155.
[2] Furusawa, K.: *Ibid.*, 1925–26, B, **99**, 155.
[3] Hewlett, A. W., Barnett, G. D., and Lewis, J. K.: J. Clin. Invest., 1926–27, **3**, 317.
[4] Liljestrand, S. H., and Wilson, D. W.: J. Biol. Chem., 1925, **65**, 773.
[5] Lindhard, J.: Skan. Arch. Physiol., 1920, **40**, 145.

followed by an absorption of 470 c.c. of oxygen per minute for 10 minutes and more. During and following the torsion the carbon dioxid combining power of the blood falls, the pH falls, due to the anaerobic production of lactic acid. The increased oxygen absorption pays the oxygen debt in the restoration of lactic acid to glycogen.

A Criticism.—There is only one criticism which I feel called upon to make with regard to the Hill-Meyerhof theory and that involves the necessary employment of carbohydrate or lactic acid metabolism for the maintenance of the circuit glycogen → lactic acid → glycogen. Every element of probability, which to my mind amounts to certainty, indicates that in the absence of carbohydrate the power for this part of the engine may be furnished wholly at the expense of the oxidation of fat.

The extraordinary tenacity with which the musculature holds its glycogen in cases in which the liver is depleted of this material has already been set forth (see p. 323). Soskin[1] has recently shown that those common means of increasing the blood sugar level, epinephrin, ether asphyxia and surgical asphyxia, will not restore the falling blood sugar level of abdominally eviscerated dogs. Muscle glycogen under such circumstances affords no relief. Soskin concludes that, in the absence of food, the liver is the sole supply of glucose to the blood. The tenacious hold of the muscle on its glycogen supply appears to be the important part of the intrinsic mechanism for muscular activity.

In the case of phlorhizination of dogs a more acute form of diabetes is obtainable than by depancreatization. Some little known experiments of A. I. Ringer[2] show the remarkable hold of the muscles of the fasting diabetic dog upon its glycogen supply. Glycogen analyses were made after 2 to 7 days of continuous glycosuria. The results in brief are as follows:

Number of dogs sacrificed	13	11	12	7	2
Days of glycosuria	2	3	4	5	7
Average glycogen in mg. in 100 gm. muscle	482	306	228	155	138
Maximum	723	499	319	315	151
Minimum	295	121	120	080	124

When one realizes that on the 5th day of phlorhizination the dog is usually comatose, has hypoglycemia, and is incapable of standing (unless given a small dose of glucose), it appears that the muscular

[1] Soskin, S.: Am. J. Physiol., 1927, **81**, 382.

[2] Ringer, A. I., Dubin, H., and Frankel, F. H.: Proc. Soc. exp. Biol. and Med., 1921, **19**, 92.

mechanism is suffering from lack of glycogen. If sugar comes from fat, why does not the animal produce it in this hour of need?

Under severe conditions of this kind these animals cannot walk on a treadmill. But Loebel, Barr, Tolstoi, and Himwich[1] induced exertion by producing strychnin hypersensibility and found an accumulation of lactic acid in the blood which was nearly equal to that produced by exercise in the normal dog. In certain of the diabetic dogs, however, muscular contractions sufficient to increase the lactic acid in the blood were unobtainable. In the light of Ringer's glycogen determinations it is probable that the facts here observed are attributable to residual muscular glycogen, both as to the origin of lactic acid from it and to the inability to secure strong muscular contractions when glycogen is present in only minimal amounts. It is not necessary to assume a production of glucose or of lactic acid from fat in order to explain the results obtained.

In concluding the evidence that fat combustion may support muscular activity the experiments of Grafe and Salomon[2] may be cited. In one of their cases of severe diabetes the metabolism of the human subject rose 218 per cent., of which increase carbohydrate as calculated from the respiratory quotient contributed only 2.5 per cent. In another case apparently no carbohydrate was oxidized as the result of muscular work, as appears below:

REST AND WORK IN SEVERE DIABETES

	Cals. per Hr.	Work in Kg.-m.	R. Q.	Urine Glucose Gm.	Glucose Oxidized Gm.
Rest	70.3	0	0.717	3.80	Trace
Work	111.6	1663	0.710	2.09	None

This is suggestive, in view of the finding of Himwich, Loebel, and Barr,[3] that in partial diabetes in human beings the breakdown of carbohydrate into lactic acid during exercise is employed just as in normal individuals.

Elsewhere arguments have been advanced against the presumption that lactic acid *per se* is oxidizable. It may be as resistant to oxidation in the healthy organism as is glucose in diabetes. Such a property would render the circuit glycogen $\rightleftarrows$ lactic acid possible in

[1] Loebel, R. O., Barr, D. P., Tolstoi, E., and Himwich, H. E.: J. Biol. Chem., 1924, **61**, 9.

[2] Grafe, E., and Salomon, H.: Deut. Arch. klin. Med., 1922, **139**, 369.

[3] Himwich, H. E., Loebel, R. O., and Barr, D. P.: J. Biol. Chem., 1924, **59**, 265.

diabetes and in fasting without having recourse to the hypothesis of sugar production from fat. One may agree with Handovsky,[1] who says, "for the conditions of lactic acid oxidation in mammalian muscle are still undefined, though of great significance for the physiology of muscle." Let us agree also with the words of A. V. Hill:

"The practice of athletics is both a science and an art, and, just as art and science are the most potent ties tending to draw men together in a world of industrial competition, so sport and athletics, by urging men to friendly rivalry, may help to avert the bitterness resulting from less peaceful struggles. If, therefore, physiology can aid in the development of athletics as a science and an art, I think it will deserve well of mankind. As in all these things, however, the reward will be reciprocal. Obviously in the data of athletic records we have a store of information available for physiological study. Apart from its usefulness, however, I would urge that the study is amusing. Most people are interested, at any rate in England and America, in some type of sport. If they can be made to find it more interesting, as I have found it, by a scientific contemplation of the things which every sportsman knows, then that extra interest is its own defense."

[1] Handovsky, H.: Biochem. J., 1926, **20**, 1114.

CHAPTER XVIII

A NORMAL DIET

Nähr dich, O Mensch, verständig! mit einem Wort erkenn dich.
Nach Liebig lern ermessen, was dir gebührt zu essen.

Als Wärmebildner merke: Fett, Zuckerstoff und Stärke,
Blutbildner sind im ganzen die Proteinsubstanzen.

Die erstern wie wir sehen, aus C, H, O bestehen,
Die letztern mannigfaltig, sind sämtlich stickstoffhaltig.

Und also iss und lebe, ersetzend dein Gewebe,
Und denk in allen Fällen, wie bild ich neue Zellen?

—Deutsche *Kommerslied* of the Time of Liebig.[1]

The principles of metabolism have been sufficiently explained in the foregoing chapters to make it possible to understand the basis of a diet which shall be physiologically rational.

It has been seen that the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms approximates 2240 calories, or 32 calories per kilogram. It is obvious that this quantity of energy must be contained in the daily food, and a little more to counterbalance the "specific dynamic" or heat-increasing power of the food-stuffs, if the individual is to be maintained in calorific equilibrium. It has been estimated that when an average mixed diet is ingested the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum (p. 282). This would amount to from 2488 to 2562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to.

Rubner[2] is authority for the following table, which indicates the energy requirement of men of various weights while doing light work:

Weight in Kg.	Area in Sq. M.	Calories of Metabolism	Calories per Kg.
80	2.283	2864	35.8
70	2.088	2631	37.7
60	1.885	2368	39.5
50	1.670	2102	42.0
40	1.438	1810	45.2

[1] Quoted by Krummacher, O.: in "Liebig als Bergründer der wissenschaftlichen Ernährungslehre," Münchener med. Wchnschr., 1923, **70**, 1124.

[2] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, p. 153.

Since man through clothing shuts himself off from the reflex action of cold on the skin, the greatest factor which tends to increase his metabolism is mechanical work, and the total amount of calories required is here dependent on the kind and the amount of the work accomplished. The requirements in this regard have already been discussed.

A point of great interest is that of the proper proportion in which the individual food-stuffs should be put together in making up a ration.

Voit defines a food as a well-tasting mixture of food-stuffs in proper quantity and in such a proportion as will least burden the organism. What is the proper proportion?

STANDARD DIETS

Voit[1] gives the following ration for the use of an average laborer, such as a soldier in a garrison—that is, for a man at work from eight to ten hours a day: Protein, 118 grams; carbohydrates, 500 grams; fat, 56 grams. This diet contains 3055 calories.

Such a ration means the food actually ingested. It is also assumed that the food-stuffs are administered in a digestible form, and are therefore completely assimilable. It has already been pointed out in the Introductory Chapter that the feces contain no undigested protein when good food is given. It is, therefore, fallacious to deduct the nitrogen of the feces from the nitrogen of the ingesta in order to determine the amount of protein assimilated. Fecal nitrogen plus urinary nitrogen together represent the waste of assimilable protein nitrogen (see p. 46).

The allowance of 118 grams of protein has provoked much discussion. The original figures were obtained by Voit by averaging the protein metabolism of many laboring men. This requirement of protein was therefore obtained by the statistical method, which simply showed what the average laborer in habit consumed. For the same class of artisan the diet given by Rubner calls for 127 grams of protein; by Atwater, 125 grams; and Lichtenfelt[2] confirms Voit's average as being the quantity of protein taken by laborers in northern Italy.

[1] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6**, Pt. 1, p. 519.

[2] Lichtenfelt, H.: Pflüger's Arch. gesam. Physiol., 1903, **99**, 1.

For men at hard labor, such as soldiers in the field, even higher quantities of protein are commended—by Voit, 145 grams; by Rubner, 165 grams; by Atwater, 150 grams. These figures again are based on statistics. Woods and Mansfield[1] found that the average protein in the ration of fifty lumbermen is 164 grams.

LOW VERSUS HIGH PROTEIN DIETS

In striking contrast to this Sivén,[2] at the age of thirty-one and a half years and weighing 65 kilograms, finds he can maintain himself in nitrogen equilibrium for a short period on a diet containing between 4 and 5 grams of nitrogen, or 25 to 31 grams of protein. In fact, in one experiment the food contained 4 grams of nitrogen, of which 2.4 grams only were in 15.4 grams of true protein and the balance in amino-acids and other nitrogenous non-protein matter of vegetable origin. Here nitrogen equilibrium was nearly attained, the nitrogen ingested being 4, and that excreted 4.28 grams. The food given, which was rich in carbohydrates, contained 2717 calories, or 43 calories per kilogram, and the total metabolism, as estimated by respiration experiments, indicated a heat production of 2082 or 32 calories per kilogram. Here was practically nitrogen equilibrium maintained at the minimum level, and a low total metabolism which was largely at the expense of carbohydrates.

It will be recalled that the quantity of nitrogen in the urine in the average fasting man who has been previously well nourished is 10 grams, a minimum which is reducible only by carbohydrate ingestion.

The experiments of Sivén did not satisfy people that a low protein metabolism was compatible with continued health and strength. Munk[3] and Rosenheim[4] both found that dogs taking a quantity of protein sufficient only to maintain nitrogen equilibrium gradually lost strength and became afflicted with digestive disturbances. These experiments fortified the idea of the benefits to be derived from a diet containing more protein than was necessary for the maintenance of nitrogen equilibrium—a *luxus* consumption. Rubner declared that a large protein allowance is the right of civilized man.

The tradition that a continued liberal allowance of protein in a diet is a prerequisite for the maintenance of bodily vigor has been

[1] Woods, C. D., and Mansfield, E. R.: "Studies of the Food of Maine Lumbermen," U. S. Dept. Agricul., Office of Exp. Sta., Bull. 149, 1904.
[2] Sivén, V. O.: Skan. Arch. Physiol., 1901, **11**, 308.
[3] Munk, I.: Arch. f. Physiol., 1891, p. 338.
[4] Rosenheim, T.: *Ibid.*, p. 341.

dispelled by Chittenden[1] and his co-workers, of whom Mendel is the most prominent.

Professor Chittenden had suffered from persistent rheumatism of the knee-joint, and determined on a course of dieting which should largely reduce the protein and the calorific intake. The rheumatic trouble disappeared, and minor troubles, such as "sick headaches" and "bilious attacks," no longer recurred periodically as before. "There was a greater appreciation of such food as was eaten; a keener appetite and more acute taste seemed to be developed, with a more thorough liking for simple foods." During the first eight months of the dieting there was a loss of 8 kilograms of body weight. Thereafter for nine months the body weight remained stationary. "Two months of the time were spent at an inland fishing resort, and during a part of this time a guide was dispensed with and the boat rowed by the writer frequently 6 to 10 miles in a forenoon, sometimes against head winds (without breakfast), and with much greater freedom from fatigue and muscular soreness than in previous years on a fuller dietary."

During the period of nine months the nitrogen of the urine was determined daily. The average was 5.69 grams. During the last two months and a half the average elimination was 5.40 grams for a body weight of 57.5 kilograms. Experiments showed that about 1 gram of nitrogen was eliminated in the feces and that nitrogen equilibrium could be maintained with dietaries of low calorific values (1613 and 1549 calories = 28 and 27 calories per kilogram) containing 6.40 and 5.86 grams of nitrogen. These figures correspond to diets containing 40.0 to 36.6 grams of protein instead of the 118 grams honored by habit and tradition. Professor Chittenden proclaimed such a diet as of the highest importance to health.

The case of Chittenden recalls a note from an early convert to the "Graham system" of vegetarianism. Sylvester Graham, in 1829, began the advocacy of moderation in the use of a diet consisting of vegetables, Graham bread (made of unbolted flour), fruits, nuts, salt, and pure water, and excluding meat, sauces, salads, tea, coffee, alcohol, pepper, and mustard. The letter reads as follows:[2] "The first three months of my experiment on the Graham system was attended by a loss of 20 to 30 pounds of flesh. Some of my neighbors

[1] Chittenden, R. H.: "Physiological Economy in Nutrition," New York, 1904.
[2] Clapp, Charles: Graham Journal of Health and Longevity, Boston, 1837, 1, 57.

expostulated with me—told me I should destroy myself by starvation, and it was even reported in a neighboring town that I had actually died from that cause. But my appetite was increasingly good and my health was increasing, and in a short time my headaches, colds, costiveness, and rheumatism left me entirely, together with my hypochondriacal and gloomy state of mind, and have not returned since, notwithstanding I have been as much exposed to wet and cold as at any period of my life."

Chittenden's experiments were not confined to an individual nor to a single group of individuals. Other experiments were made on professional men, on student athletes in training, and on soldiers under military *régime*. The daily nitrogen in the urine in periods extending from five to nine months averaged as shown in the table given below in the individuals belonging to the three groups.

At convenient periods during the experiments it was determined that the body was being maintained in nitrogenous equilibrium on the diet which gave rise to the stated amounts of urinary nitrogen (see p. 364).

The professional group alleged a greater keenness for its work, the athletic group won championships in games, and the soldiers maintained perfect health and strength, many professing repugnance to meat when they were allowed it after five months of practical abstinence.

Professors and Teachers		University Athletes		United States Soldiers	
Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.
57.0	5.69	71.0	9.37	62	7.42
70.0	6.53	61.0	10.41	59	7.03
65.0	7.43	78.0	8.88	60	7.26
65.0	8.99	83.0	9.04	58	8.17
61.5	8.58	62.0	7.47	60	8.39
		56.0	7.58	53	7.13
		73.0	10.09	71	8.91
		75.0	11.06	72	7.84
				62	8.05
				59	7.38
				55	8.25
				65	8.08
				57	8.61

Although it is possible that the alleged improved mental condition[1] may have been due to suggestion (p. 682), still the fact remains

[1] Chittenden, R. H.: *Loc. cit.*, p. 51.

that it has been proved by Chittenden's work that the allowance of protein necessary for continued health and strength may be reduced during many months to half or less of what the habit of the appetite suggests.

It remains to be seen whether this quantity of protein in the ration, which is not greater than the body would metabolize in starvation, is advisable as a program for the whole of one's adult life.

The foods with the strongest flavors are meats, which therefore add relish to a repast and stimulate the digestive secretions.

Chittenden believes that the large quantity of protein in an ordinary diet is due to self-indulgence. He protests against such indulgence, and thinks that a needless strain is thereby imposed upon the liver, the kidneys, and other organs concerned in the transformation and elimination of the end-products of protein metabolism.

Another advocate of a low protein dietary has arisen in the person of Hindhede,[1] who advocates as ideal a diet consisting of bread, potatoes, and fruit, together with a small quantity of milk when this latter is obtainable. It is avowedly a "back-to-the-farm" dietary. Splendid health, both of body and mind, and the peasants' comparative immunity to indigestion, kidney and liver disease, to diabetes, as well as an absolute immunity to gout, is the alluring prospect held out by the following dietary:

Graham bread	500 grams.
Potatoes	1000 "
Vegetable margarin	150 "
Apples	600 "
Milk	500 c.c.

Such a diet gives a urine which dissolves uric acid readily, the addition of the apples appreciably increasing this power. Hindhede also states that the ingestion of 5 kilograms of tomatoes with 600 grams of Graham bread and 150 grams of margarin daily for four days also produces a urine having a good solvent power over uric acid.

In analyzing the effect of the factors of the bread-potato-fruit diet Hindhede found that an exclusive bread diet gave a urine which exhibited a strong tendency to deposit uric acid, and notes that the Russian peasant, who works fourteen to sixteen hours daily and lives almost exclusively upon bread, frequently has gravel. On the other hand, potatoes when ingested yield a urine which is very slightly

[1] Hindhede, M.: Skan. Arch. Physiol., 1912, **27**, 87.

acid, often on the border-line of alkalinity, and one which has a very solvent power over uric acid.

It is a curious fact that the potato, long proscribed by many physicians, has decided therapeutic value. Some one has remarked, "One meets the potato today in the very best circles."

Hindhede[1] reports the following results upon the daily nitrogen balance after giving various forms of bread during periods of eight days:

	In Diet		
	Calories	N Grams	± N to Body, Grams
Schwarzbrot 1000 g. + fat 120 g.....	3200	12.1	+0.3
White bread 900 g. + fat 120 g.....	3640	13.2	+0.6
Rye bread 1000 g. + fat 135 g.....	4000	12.8	−1.7
Graham bread 1000 g. + fat 140 g.....	3800	15.1	+0.4

These results show a favorable utilization of bread protein.

Concerning the utilization of potato protein Hindhede[2] reports the following remarkable experiment: An individual partook of a diet of 2 to 4 kilograms of potatoes with some margarin daily during a period of nearly three hundred days. The potatoes were well boiled in water and the water in which they were cooked was drunk on account of valued salts therein contained. The rule was to eat only when hungry. Potatoes could be eaten at the rate of 100 grams in four minutes. Stools were passed once every three or four days, but there was no constipation. During a period of one hundred and seventy-eight days 6.05 grams of nitrogen and 3725 calories were contained in the daily diet, and there occurred an average daily loss of body nitrogen of 0.42 gram. During a second period of ninety-five days, when mechanical work was performed, there were 8.45 grams of nitrogen and 4900 calories in the daily diet and the daily loss of body nitrogen was 0.36 gram. During these ninety-five days the food supply consisted of 350 kilograms of potatoes and 22 kilograms of fat taken in the form of margarin. (See page 58.)

Hindhede states that he "feels weak" after taking much meat.

Enthusiastically Hindhede[3] proclaims, "That it is cheaper to live directly upon the products of Mother Earth rather than to first put them through cattle, is so self-evident that no one can deny it. It will however surprise most physicians to learn that it is also the most healthy manner of life."

[1] Hindhede, M.: Skan. Arch. Physiol., 1913, **28**, 165.
[2] Hindhede, M.: *Ibid.*, 1913, **30**, 97.
[3] Hindhede, M.: *Ibid.*, 1925, **47**, 102.

On the other hand, let us recall the words of William Stark, M.D. (1740–1770) who, instigated by "Dr. B. Franklin of Philadelphia," twice induced scurvy in himself by taking a diet of bread and water, the second attack of scurvy proving fatal. Dr. Stark says:

"A very spare and simple diet has commonly been recommended as most conducive to health, but it would be more beneficial to mankind if we could shew them that a pleasant and varied diet was equally consistant with health as the very strict regimen of Cornaro or the Miller of Essex. These and other abstemious people, who having experienced the great extremities of bad health, were driven to temperance as their last resource, may run out in praises of a simple diet, but the probability is that nothing but the dread of former sufferings could have given them resolution to persevere in so strict a course of abstinence."

One may let this introduce the other side of the story.

Lichtenfelt[1] shows that while there is no statistical difference in the height of individuals as due to occupation, still the people of southern Italy are not so large nor so well developed physically as their fellows of northern Italy. He explains this stunted growth as due to a low protein and calorific intake in the food.

Albertoni and Rossi[2] describe how the poorest Italian peasants in southern Italy lived on cornmeal, green stuffs, and olive oil, and have done so for generations. There was no milk, cheese, or eggs in their dietary. Meat in the form of fat pork was taken three or four times a year. Cornmeal was taken as "polenta," or was mixed with beans and oil, or was made into corn-bread. Cabbage or the leaves of beets were boiled in water and then eaten with oil flavored with garlic or Spanish pepper. The average elimination of urinary nitrogen of 13 persons in three families when taking this diet was for men 8.1 and for women 6.7 grams of nitrogen daily. The investigators, furthermore, considered a family of 8 individuals of whom 2 were children. The annual income was 424 francs or $84. Of this, 3 cents per day per adult was spent for food and the remaining $\frac{3}{5}$ cent daily was spent for other purposes. The addition of 100 to 200 grams of meat daily to the diet of each of these individuals increased their muscular power, their power to utilize vegetables, and the investigators believed that such an addition was essential to mental health as well.

[1] Lichtenfelt, H.: Pflüger's Arch. gesam. Physiol., 1905, **107**, 57.
[2] Albertoni, P., and Rossi, F.: Arch. exper. Path. u. Pharm., 1908, Suppl., p. 29.

Campbell[1] has investigated the urinary nitrogen output of individuals of various races attending the medical school at Singapore and finds the following values:

Brahmin	5.1	Malayan	8.7
Hindoo	6.0	Tamil	9.3
Bengali	7.6	Eurasian	9.9
Chinese	8.6	European	11.7
Sikh	8.6		

The Brahmin and Hindoo were strict vegetarians except for the taking of a little milk.

Denis and Borgstrom[2] find that the average urinary nitrogen of 233 male medical students at Tulane University in semi-tropical New Orleans is 12.6 gm. (+10 per cent. for fecal N = 73.8 gm. protein). It was higher than this during the cooler months. Great numbers of medical students in New York City do not have an output in excess of 12 gm. of urinary nitrogen daily.

The position of the food extremists was powerfully attacked by Rubner,[3] whose general tone was in advocacy of variety in the dietary of man in accordance with prevailing habits and certainly without attempting to conform to a protein minimum.

Hirschfeld[4] finds that the actual ration of a German soldier contains 98 grams of protein, with no untoward results. He states that writers on economics, who believe the German populace underfed because they do not have 118 grams of protein daily, are unduly pessimistic.

Although, as has been stated, the battleground has been over the allowance of 118 grams in Voit's dietary, it will be surprising to many to learn that Voit himself said little on the subject. He[5] showed that a vegetarian can live in nitrogenous equilibrium on a diet containing 48.5 grams of protein and that an active working man weighing 74 kilos may get along on less than 118 grams. He discouraged the tendency to eat meat in excess. He also discouraged the practice of vegetarians who overload the digestive tract with the coarser kinds of vegetable foods which leave large indigestible residues.

It is not to be denied that 50 grams of protein (containing 8 grams of nitrogen) are apparently able to maintain the adult body machine

[1] Campbell, J. A.: Biochem. J., 1919, **13**, 239.
[2] Denis, W., and Borgstrom, P.: J. Biol. Chem., 1924, **61**, 109.
[3] Rubner, M.: "Ueber moderne Ernährungsreformen," Berlin, 1914.
[4] Hirschfeld, F.: Arch. f. Physiol., 1903, p. 380.
[5] Voit, C.: Z. f. Biol., 1889, **25**, 278.

in perfect repair. Vegetarians, fruitarians[1] (who live on fruit and nuts), and vigorous adults, who largely exclude protein from the diet, are evidently able to live in health and strength upon this quantity. It must be, however, that more than this amount is advisable during growth or convalescence from wasting disease, or during the muscular hypertrophy which accompanies preliminary training for athletic effort.

Abderhalden[2] mentions the fact that since various body tissues are constructed of different proteins, therefore a large variety of amino-acids in sufficient quantity must be available for their proper replenishment. Hence, it is reasonable to assume that an excess of food protein is essential to supply the special amino-products for the synthesis of the characteristic proteins of the blood-serum and those of the different organs.

It is certain that large ingestion of protein in hot weather increases the heat production with accompanying increase in perspiration (p. 280). Meat should therefore be avoided in hot weather. In cold weather such an extra heat production may produce a pleasurable sensation of warmth. Dr. Folin, in personal conversation with the writer, said that a dietary of carbohydrates, fat, and low protein was easily borne by an individual during the summer, but during the winter the man complained of his sensitiveness to cold when taking the same diet.

Ranke[3] describes experiments on himself (weight = 73 kilograms) during the hottest months of summer weather in Munich, at which time he partook of an ample diet, rich in protein (135 grams), containing 3300 calories—a diet which he had enjoyed during the preceding winter. He had to force himself to eat. He was first attacked by catarrh of the stomach, from which he recovered by dieting, and subsequently became infected by diphtheria. He had formerly suffered from catarrh of the stomach while residing in the tropics. The excess of food, and especially of protein, threw an unnecessary burden upon the heat-regulating apparatus which would not have taken place had the dictates of the appetite been allowed full sway and had the ration voluntarily been reduced.

Chittenden and Lusk crossed the English Channel together on March 20, 1918. Both had been taking for several weeks the greatly

[1] Jaffa, M. E.: U. S. Dept. Agricul., Office Exp. Sta., Bull. 132, 1903.
[2] Abderhalden, E.: Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs., 1906, **1**, 225.
[3] Ranke, K. E.: Z. f. Biol., 1900, **40**, 299.

restricted British civilian diet of the time. The meat equivalent of 4 small chops a week had not been exceeded. On the naval transport "military rations" were allowed and Lusk partook of a large slice of English cold roast beef to his delight and satisfaction. This sensation he attributed to the replenishment of the "improvement quota" of his protein stores, while Chittenden was inclined to attribute the result to the appetite creating stimulus action of the sea air. Both opinions are proper themes for psycho-analysis. Perhaps roast beef for Sunday dinner fills a real need.

From the knowledge at hand there appears to be no strongly substantiated argument why that portion of mankind living in a cool climate should not follow the general custom of taking 100 grams of protein, more or less, in moderate accordance with the dictates of their appetites. Everyone knows that excessive ingestion of highly flavored meats results in jaded appetite, an automatic signal of excess.

A similar excess of food when given to dogs results in vomiting. Rubner[1] says that many years of experience with dogs leads him to believe that appetite and capacity for digestion and absorption depend on the dog's requirement for energy in his given state of nutrition. A diet which a dog will greedily devour when in a room at a temperature of 0° he will in part refuse when at a temperature of 33°.

In this connection it may be mentioned that Newburgh and Clarkson[2] have found that rabbits, after prolonged ingestion of meat given in diets containing protein to the extent of 36 per cent., develop *atherosclerosis*, a disease of the arteries which is a primary lesion of the intima.

In rats the ingestion of protein in large quantity does not damage the kidney[3] but causes it to hypertrophy.[4] Urea fed in equivalent amount fails to bring about this hypertrophy.[5]

In 1913 Krogh and Madam Krogh[6] published a volume regarding their scientific investigations in Greenland of the dietary habits of the Eskimos. The diet of this race was strictly carnivorous, consisting of seal meat and the meat of reindeer, walruses, and whales.

[1] Rubner, M.: "Energiegesetze," 1902, p. 83.
[2] Newburgh, L. H., and Clarkson, S.: Arch. Int. Med., 1923, **31**, 653.
[3] Miller, A. J.: J. Exper. Med., 1925, **42**, 897.
[4] Addis, T., MacKay, E. M., and MacKay, L. L.: J. Biol. Chem., 1926–27, **71**, 139.
[5] Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C.: *Ibid.*, p. 317.
[6] Krogh, A., and Krogh, M.: "A Study of the Diet and Metabolism of Eskimos," Copenhagen, 1913.

Eskimos have great capacity for physical endurance and resistance to cold, and gout and arthritis are unknown among them. W. A. Thomas[1] lists the foods of the Eskimo as being the meat of whale, walrus, seal, caribou, musk ox, arctic hare, polar bear, ptarmigan, and the numerous sea birds, geese, ducks, awks, gulls, etc., and finally fish. These are all eaten raw. Little fat and blubber are eaten but are used for oil in lighting and warming. The Eskimo eats the liver, except polar bear liver which is poisonous and which the dogs refuse to touch even though they be starving. Thomas summarizes his report as follows:

"The Greenland Eskimo, on a carnivorous diet, exhibits no increased tendency to vascular and renal disease. This diet furnishes him with vitamins adequate for protection against scurvy and rickets, while the Labrador Eskimo, whose meat is cooked and whose diet includes many prepared, dried and canned articles, is very subject to both these maladies."

Vilhjalmur Stefansson in 1921 published a book entitled "The Friendly Arctic." He has lived eleven and a half years within the arctic circle and of that total time nine years were lived while taking a strictly carnivorous diet. He once lived nine successive months partaking of an exclusive meat diet. Lieb[2] reports that he is in perfect physical condition. Stefansson states in his book that there is probably no field of human thought in which sentiment and prejudice take the place of sound judgment and logical thinking so completely as in dietetics.

It would be futile to dilate upon this aspect of the case, filled as it is both with comedy and tragedy. Those who are interested will, however, find the subject of dietetics admirably handled by Professor Mary S. Rose.[3]

Evvard[4] writes: "When the appetite is given full control of what shall be eaten it is surprising to note how pigs naturally select the specific feeds which swine herdsmen have long since approved of as the best, and, what is equally surprising, the pigs show a marked avoidance of those feeds usually considered as ill adapted to swine."

The same instinctive choice of the superior food above the inferior food applies to rats and mice.[5]

[1] Thomas, W. A.: J. Am. Med. Assn., 1927, **88**, 1559.
[2] Lieb, C. W.: *Ibid.*, 1926, **87**, 25.
[3] Rose, M. S.: "Fundamentals of Nutrition," New York, 1927.
[4] Evvard, J. M.: Proc. Iowa Acad. Sc., 1915, **22**, 400.
[5] Mitchell, H. S., and Mendel, L. B.: Am. J. Physiol., 1921–22, **58**, 211.

THE DIVISION OF THE FOOD-STUFFS

While the protein quantity in the diet may vary within wide limits with the taste, the purse, or the fad of the individual, the quantity of energy required by the organism is a remarkably constant factor, being 35 calories per kilogram of body weight in the average man doing light work on a mixed diet. Comparatively little of this energy is furnished by protein.

In a fasting individual protein furnishes 13 and fat 87 per cent. of the total heat given off from the body.

In Voit's medium mixed diet, designed for a laboring man, the 118 grams of protein furnish about 15 per cent. of the total of 3055 calories.

In such an experiment as Sivén's, mentioned on page 449, which represents a very low level of nitrogen equilibrium, the 25 grams of protein ingested furnished 100 calories out of 2717 ingested in the food, or 3.6 per cent. However, since the total metabolism was measured as 2082 calories, the protein furnished approximately 5 per cent. of this energy.

Chittenden[1] gives a dietary containing 50 grams of protein and 2500 calories as sufficient for a soldier at work. This allows 8 per cent. of the total energy in protein. These data may be thus summarized:

	Grams of Protein in Diet	Calories from Protein Metabolism in Per Cent.	Calories from Fat and Carbohydrate Metabolism in Per Cent.
Starvation	0	13	87
Voit's standard (liberal protein)	118	16	84
Chittenden's standard (reduced protein)	50	8	92
Sivén's minimum	25	5	95

Chittenden's diet conforms to that of the Chinese or the Bengali, that of Sivén to the vegetarian diet of the Brahmin or Hindoo. On the other hand Krogh and Krogh find that the Eskimo ingests 282 gm. of protein daily or 44 per cent. of the total caloric intake.

The energy other than that contained in protein may be given as carbohydrates or as fat. Voit allows a laborer 500 grams of starch (2050 calories, or 67 per cent. of the total) as the quantity which the intestinal canal may readily digest, and adds 56 grams of fat (521 calories, or 17 per cent. of the total) to the diet.

It has already been observed that ninety per cent. of the energy derived from non-protein sources may be given in fat and ten per

[1] Chittenden, R. H.: *Loc. cit.*, p. 254.

cent. in carbohydrates without affecting the carbohydrate power of economy over the protein metabolism (see p. 353).

DIET AND MUSCULAR WORK

This part of the subject really becomes a mere matter of calculation of the requirement of the resting organism, and the addition thereto of sufficient energy to accomplish the mechanical work.

How this is done has in part been set forth in another chapter. A bicyclist riding for sixteen hours may have a metabolism amounting to 9000 calories daily, and the average ration of a Maine lumberman may rise to a value of 8000 calories. Champion wrestlers in a world's contest[1] may ingest daily during their periods of effort diets containing protein 217.9 grams (35.1 grams of N); fat, 259.5 grams; carbohydrates, 431 grams; together, 5070 calories; or protein, 182.2 grams (29.2 grams N); fat, 204.6 grams; carbohydrates, 392.3 grams; together, 4254 calories. Much cream was taken by these last-named individuals.

A long-distance run from Milwaukee to Chicago, a distance of 80 miles (128 kilometers), has been accomplished in 15 hours at the rate of 5.3 miles per hour. If the individual weighed 70 kg. his metabolism would have been as follows (data on p. 432):

	Calories
Basal metabolism 24 hours	1680
Required to move 70 kg. 141.5 meters per minute for 15 hours	7180
Total for running and sleeping	8860

This effort of running 5.3 miles requires 480 calories per hour in contrast with an expenditure of 554 calories for swimming 2 miles per hour, a possible rate in buffeting the waters of the English Channel (see p. 437). The maximal capacity of human endurance appears to be quite constant.

Adding to the calorie values needed for work, the basal metabolism of 70 calories, one may contrast the following energy expenditures:

	Cals. per Hr.
Bicycle riding, century run	600
Running 5.3 miles per hr.	550
Swimming 2 miles per hr.	624
Climbing Pike's Peak (see p. 589)	767

The energy expended in strong sustained effort seems to be in each form of movement approximately the same. The bicycle rider

[1] Lavonius, H.: Skan. Arch. Physiol., 1905, **17**, 196.

rode to exhaustion. The runner established a long-distance record for the course, the mountain climber made a record ascent, while the calculation for the swimmer, though based on only one observation, is inserted for the sake of completeness. About 600 calories per hour is in the neighborhood of the body's capacity for sustained work.

Liljestrand and Stenström[1] are authorities for the statement that to walk briskly, to run, or to ski, requires about the same amount of energy to move 1 kg. of body weight 1 meter forward. To skate requires one-half and to bicycle one-third this amount of energy for the same unit of accomplishment.

The mild form of amusement known as "ping pong" calls for a total expenditure of energy amounting to 312 calories per hour for a man weighing 70 kg.

Carl Tigerstedt and Olin[2] report that to do a physiological experiment upon a frog's muscle requires an energy expenditure 96 per cent. above the basal metabolism and 47 per cent. above the metabolism when sitting at rest at a table. Reading aloud increased the metabolism between 2 and 44 per cent. above the sitting metabolism, depending on the power of the voice.

It was Lavoisier[3] 140 years ago who wrote, "One can learn, for example, how many pounds of weight lifting correspond to the effort of one who reads aloud or of a musician who plays a musical instrument."

We now have the following analysis[4] of the work of a pianist:

THE WORK OF PIANISTS

	Movements (Both Hands) per Sec.	Pulse per Min.	Calories per Hour	Increase Per Cent.
Rest	....	67	53	
Mendelssohn (Songs)	3.3	72	95	78
Beethoven (*Appassionata*)	7.9	84	128	140
Chopin (*Etudes*)	14.5	84	146	174
Liszt (*Tarentella*)	10.5	92	158	200

The time devoted to playing varied between 8 minutes for Liszt and 22 minutes for Beethoven. To these results may be added those obtained by Loewy and Schroetter:[5]

[1] Liljestrand, G., and Stenström, N.: Skan. Arch. Physiol., 1920, **39**, 167.
[2] Tigerstedt, C., and Olin, H.: *Ibid.*, 1924, **45**, 82.
[3] Lavoisier, A. L.: Mémoires de l'académie des science, 1789, p. 185.
[4] Okunewski, J. L.: Arch. f. Hyg., 1924, **94**, 143.
[5] Loewy, A., and Schroetter, H.: Pflüger's Arch. gesam. Physiol., 1926, **211**, 1.

EXPENDITURE OF ENERGY IN MUSICAL PERFORMANCE

	Increase		Details
	Per Cent.	Cals. per Hr.	
1. Reading, 4 persons	41–47	27–33	
2. Singing	19	11	Brahms, *Ewige Liebe*, low voice
	83	56	Obermeyer, *Rheinlied*, loud voice
3. Piano	47	40	Schubert, *Impromptu*
	270	188	Liszt (powerful effort)
4. Violin	64	46	Sarasate, *Zigeunerweisen*
5. Cello	129	89	Difficult piece
6. Musical conductor	53	44	Rossini, Prelude to *Wilhelm Tell*
	118	95	Liszt, *Les Préludes*

It is evident that notable increases in metabolism are associated with musical performance.

Also the metabolism during dancing has been measured[1] and for a man of 70 kg. the following results are reported:

Waltz	280 cals. per hour
Fox trot	335 " " "
Polka	529 " " "
Mazurka	761 " " "

It is evident that in violent dancing the metabolism may reach the height represented by the maximum of human muscular power. It reaches the same level as in a man sawing wood.

Atwater[2] reports the following dietaries for farmers:

	Calories
Farmers in Connecticut	3410
" Vermont	3635
" New York	3785
" Mexico	3435
" Italy	3565

To this list may be added for farmers in Finland 3474 calories, as found in the exhaustive studies of Sundström.[3] He states that the diet of the average Finnish peasant contains 136 grams of protein, 83 grams of fat, and 580 grams of carbohydrates, which corresponds to a division of calories so that protein furnishes 15 per cent., fat 21 per cent., and carbohydrates 64 per cent. of the total. He notes that if the peasant's requirement of energy were taken in rye bread alone 124 grams of protein would be ingested with it, whereas if a milk

[1] Grönholm, G., Sandbacka, I., Stenros, O. G., and Ylänkö, V.: Skan. Arch. Physiol., 1926, **48**, 125.

[2] Atwater, W. O.: Report of Storr's Agricultural Station, 1902–03, p. 135.

[3] Sundström, S.: "Untersuchungen über die Ernährung der Landbevölkerung in Finnland," Helsingfors, 1908.

diet covered the requirement 195 grams of protein would be taken. He, therefore, sees no outlook for a low protein dietary among the poorer classes, that have hard work to do and must ingest large quantities of food fuel.

Woods and Mansfield[1] report a dietary study of a camp of fifty Maine lumbermen actively engaged in chopping and yarding logs. The investigation continued for six days. The daily average ration per man was as follows: Protein, 164.1 grams; fat, 387.8 grams; carbohydrates, 982.0 grams; calories, 8083. This dietary would appear almost fabulous were it not for the fact that Atwater has actually shown that a metabolism equivalent to 9300 calories a day may be produced by a man riding a stationary bicycle for sixteen hours.

FOOD IN INDUSTRIAL PURSUITS

In 1918 when the question of the nutrition of peoples was agitating the world an analysis of the food requirements of people occupied in industry was made.[2] The statistical averages for the weight of men and women of a given height at 35 years of age were taken from the report of the medicoactuarial investigation of 1912. The statistics for the group of men were based on 221,819 individuals. The basal metabolism of such average men and women was calculated according to Du Bois. To the calories of the basal metabolism was added 10 per cent. during a period of 16 hours in order to provide for work of standing or sitting in a chair. The studies of Becker and Hämäläinen,[3] showing the extra calories per hour attributable to various occupations were then available, as were those of Carpenter[4] for typewriting. These are given below:

EXTRA CALORIES PER HOUR ATTRIBUTABLE TO OCCUPATIONS OF MEN

Occupation of Men	Extra Calories of Metabolism per Hour Due to Occupation
Tailor	44
Bookbinder	81
Shoemaker	90
Metal worker, filing and hammering	141
Painter of furniture	145
Carpenter making a table	164
Stonemason chiseling tombstone	300
Man sawing wood	378

[1] Woods, C. D., and Mansfield, E. R.: *Loc. cit.*
[2] Lusk, G.: J. Am. Med. Assn., 1918, **70,** 821.
[3] Becker, G., and Hämäläinen, J. W.: Skan. Arch. Physiol., 1914, **31,** 198.
[4] Carpenter, T. M.: J. Biol. Chem., 1911, **9,** 231.

EXTRA CALORIES PER HOUR ATTRIBUTABLE TO OCCUPATIONS OF WOMEN

Occupation of Women	Extra Calories of Metabolism per Hour Due to Occupation
Seamstress, needle work	6
Typist, 50 words per minute	24
Seamstress, using sewing machine	57
Bookbinder	63
Housemaid (moderate work*)	81
Laundress (moderate work)	124
Housemaid (hard work*)	157
Laundress (hard work)	214

* Cleaning windows and floors, scouring knives, forks and spoons, scouring copper and iron pots.

It was easy to superimpose these values, calculated for an 8-hour day, upon the basal metabolism (plus 10 per cent. for 16 hours of activity) of men and women of different weights and heights. The results are given in the two accompanying charts (Figs. 26 and 27).

To these values must be added (*a*) 200 and 150 calories per day for men and women, respectively, for such movements as are involved in dressing and undressing and other extra motions not definitely measurable; and (*b*) 150 to 200 calories for every hour of walking at the rate of 3 miles (4.9 kg.-m.) per hr. to and from the place of occupation.

Although these results did not by any means cover the industrial situation, yet meager though they were, they afforded a basis for the study of various pressing war-time problems.

Late Work of Rubner's Laboratorium für Arbeits-Physiologie.—Atzler,[1] with great personal ability and thoroughness, under the guiding genius of Rubner's master mind, has attacked the problem of industrial efficiency. He quotes Durig[2] as follows:

"This rapid loss in physical power is typical of the industrial worker, while the farmer retains his strength undiminished far into old age. A true proof of the social value of a system is the length of life before invalidism. The longer this period extends, the better one finds the working and living conditions to have been. Of course, there are many other factors which are not in the realm of physiological research but which are responsible for the premature exhaustion of the industrial worker. These include unhygienic shops, industrial diseases, unhealthy homes, bad habits of life, the desolating effects of alcoholism, and other excesses. Also psychical influences, the

[1] Atzler, E., Herbst, R., and Lehmann, G.: Biochem. Z., 1923, **143**, 10.
[2] Durig, A.: "Die Ermüdung," Vienna, 1916.

monotony of much machine labor, the noise of the machines, worry for the future, the compulsion to work, and many other mental influences

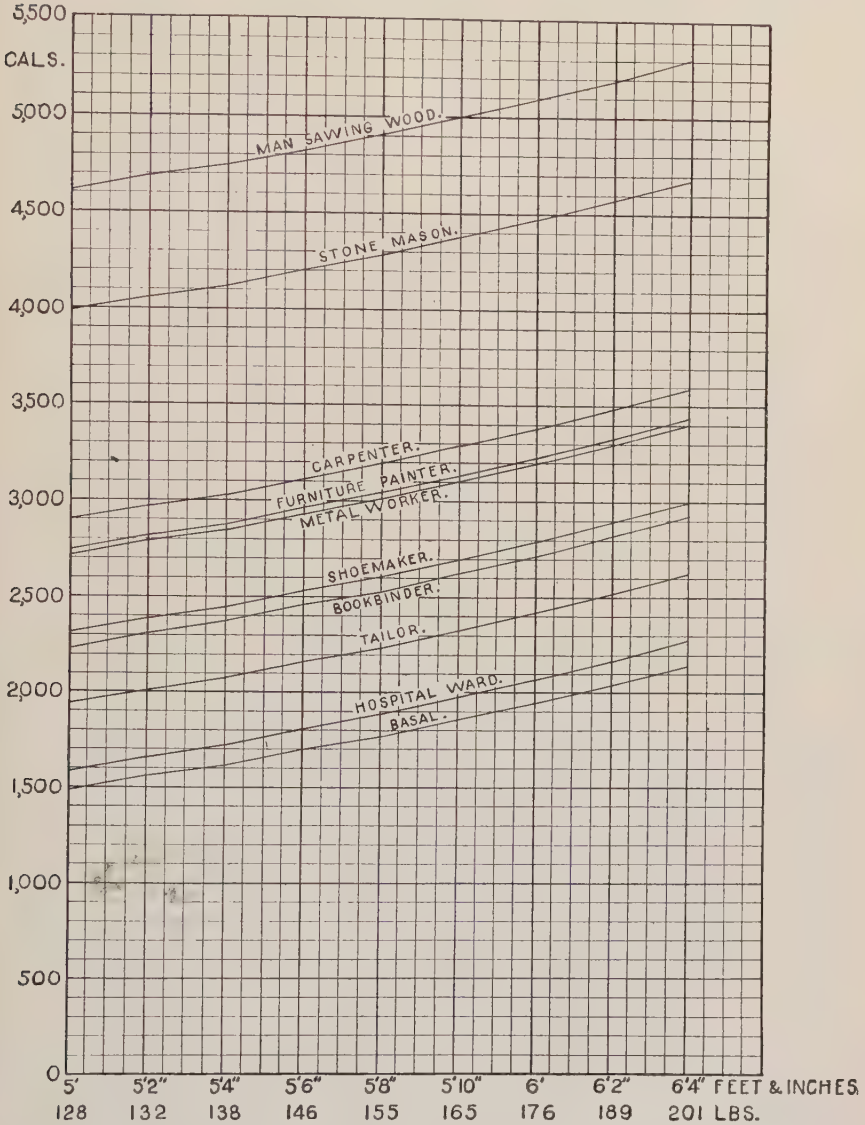


Fig. 26.—Metabolism in calories per day of men engaged for eight hours in various industrial pursuits (Lusk).

can act upon the duration of the period of joy in work and thereby also reduce the power to work. We know that work accomplished

against personal wish requires a greater expenditure of energy than that accomplished out of love and desire."

Atzler states that the maximum physical power of the industrial worker in Germany is reached at 40 years of age for the man and at

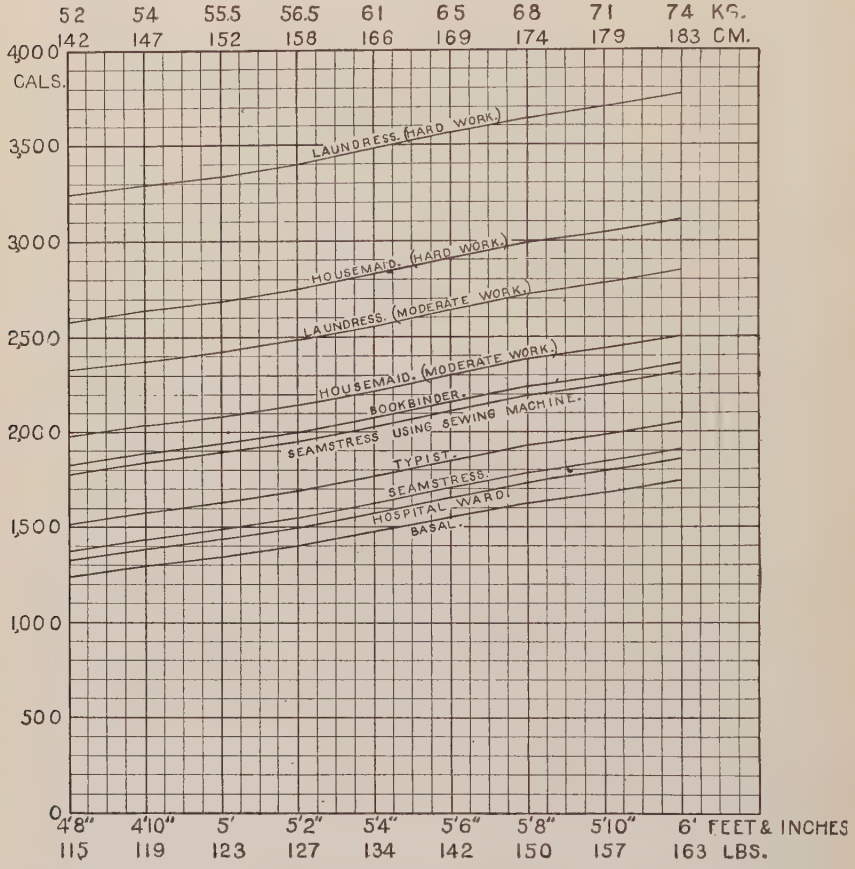


Fig. 27.—Metabolism in calories per day of women engaged for eight hours in various industrial pursuits (Lusk).

35 years for the woman, after which it declines. He then continues as follows:

"It is therefore important to consider the machinery of the workman himself. Intensity of work must not involve the psychical ruin of a people. The modern industrial state tends to be associated with racial degeneracy. This decline is accentuated by the fact that

the highly educated have an average of 1.5 children, while the lowest classes and criminals have 7 children. Also the trades union system suppresses the activities of the highly gifted worker. An American engineer, Taylor, concluded that workmen had a natural instinct toward physiological laziness. He found what the best men could do and fixed high pay for this maximum accomplishment. This stimulated the others to seek equal rewards. He also attempted to relieve the worker from unnecessary movements. The worker had purely mechanical work to do, without thought being necessary, and he was stimulated to work with his whole power. This method raised the production enormously. But although there were important points of value in his system, it tended to the early annihilation of the workman's physical power. Taylor was an engineer; he understood the methods of the dead machine, but not those of a living motor like man. Taylor sought for the maximal output of energy, whereas our experiments have been to discover the optimum. How does the living motor work with greatest economy?"

The researches of Atzler upon economy in walking have already been cited (p. 433). Among many detailed experiments which he has performed one may perhaps dwell especially on his investigation into the efficiency of work when a man revolves a crank attached to the pedal of a bicycle ergometer and upon the efficiency of a man in lifting weights.

In analysis of the work done with the ergometer consideration was given to the height of the axle from the ground, the radius of the crankshaft, and the work done in kilogrammeters per revolution. The man respired into a Benedict respiration apparatus during each experiment. It was found that when the radius of the crankshaft was 28.4 cm., when the height of the axle from the ground was 114.3 cm., and the work in kg.-m. 13.0 per revolution, then 1 kg.-m. of work was accomplished at the minimum cost of 11.7 calories or an efficiency of 20 per cent. for the working muscle of the human arm. When the height of the axle was raised to 162.2 cm. from the ground and the work was increased to 32.5 kg.-m. per revolution, then to accomplish 1 kg.-m. of work required 33.5 calories, an efficiency of only 7 per cent. The subject, when turning the crank, had to stand on tiptoe to do so when the shaft was at its highest. The axle can not be put too high or too low without loss of economy of human power. A table giving a summary of the results follows:

GRAM CALORIES REQUIRED TO ACCOMPLISH 1 KG.-M. OF WORK EXPENDED BY THE ARMS ON A CRANK ATTACHED TO A BICYCLE ERGOMETER, INCLUDING AS VARIABLES (a) HEIGHT OF AXLE FROM THE FLOOR, (b) RADIUS OF THE CRANKSHAFT, (c) WORK IN KG.-M. ACCOMPLISHED IN ONE REVOLUTION OF THE AXLE

Height of Axle from Floor	Radius of Crankshaft	Work in Kg.-M. per Revolution				
		6.5	13.0	19.5	26.0	32.5
		Cals.	Cals.	Cals.	Cals.	Cals.
55.3	19.4	20.7	15.8	16.5	18.7	23.3
	28.4	22.3	14.6	13.2	13.8	17.1
	36.6	27.8	16.5	13.8	14.4	16.5
82.7	19.4	17.8	14.5	15.5	17.8	26.0
	28.4	19.4	15.0	12.5	14.2	15.7
	36.6	26.1	15.5	13.9	13.5	14.6
114.3	19.4	14.6	14.1	18.3	25.1	
	28.4	13.6	11.7	12.5	14.3	17.5
	36.6	17.0	13.5	12.4	12.1	14.2
162.2	19.4	14.5	17.4	23.5	28.9	
	28.4	20.3	19.2	19.0	22.6	33.5
	36.6	22.0	18.4	18.5	20.5	22.2

With the axle high in the air the man works uneconomically. When it is low down near the floor the man must bend his body with each revolution, but when the axle is just above the navel the greatest economy of result is obtained because auxiliary movements of the body are obviated. The worker naturally selects 18 revolutions per minute, but these are too few to be most economical. The optimal rapidity is 35 revolutions per minute. In this connection A. V. Hill is quoted as stating that a maximal muscular contraction lasts 0.7 second followed by 1 second of rest.

Atzler notices a profound influence in training. A reduction in the energy needed of 37 per cent. is thereby induced.

The lifting of light weights of 1.4 to 2.8 kg. to a height of 1 meter is accomplished at an expense of 24.7 gram calories per kg.-m. of work, which is in exact accord with the value 24.9 gm-cal. obtained by Hanriot and Richet[1] in 1887.

Continuing this line of investigation, Atzler[2] has measured the energy requirement of a man who lifts heavier weights, balls weighing 9.15, 13.85, and 28.56 kg. These were lifted from the floor and from given heights to differently arranged heights. The results are given in the table.

[1] Hanriot, M., and Richet, C.: Compt. rend. soc. biol., 1887, **105**, 76.
[2] Atzler, E.: Technik und Wirtschaft, 1924, No. 8, 173.

GRAM CALORIES REQUIRED TO LIFT 1 KG. 1 METER FROM THE FLOOR OR FROM GIVEN HEIGHTS FROM THE FLOOR TO DIFFERENT MEASURED LEVELS

Original Height	Height Lifted	Kg. Weight Lifted		
		9.15	13.85	28.56
Cm.	Cm.	Cals. per Kg.-m. Work		
0	50	76.8	57.6	42.9
	100	59.3	47.3	42.1
	150	48.3	39.0	39.7
	200	44.5	37.3	40.7
50	50	50.7	42.6	41.2
	100	38.7	33.5	38.6
	150	36.2	31.9	38.7
100	50	31.9	29.3	41.0
	100	32.4	29.4	35.5
150	50	38.3	32.9	50.9

It is evident that it is easiest and most economical to lift a weight from a position 1 meter in height rather than to lean down, pick it up from the ground, and raise it to a higher position. Thus, to raise a ball weighing 13.85 kg. from the ground to a height of 2 meters requires 37.3 calories per kg.-m. of work done, and to raise it from a table 1 meter high to a shelf 2 meters high requires only 29.4 calories. This is a saving of 21 per cent. of the workman's energy. It represents the scientific interpretation of the endless belt system in the modern automobile factory.

THE FOOD OF THE SOLDIER

Chittenden at one time recommended 2500 to 2600 calories daily as sufficient for a soldier at drill. On the other hand, the ration of a United States cavalryman at the outbreak of the war contained over 8000 calories. At a meeting called at Washington in 1917 the War Department was told that such a ration meant a trail of bacon thrown away wherever the cavalryman went.

It was not difficult to compute from known data about what the seasoned soldier (70 kg.), carrying his equipment (20 kg.), would require for a forced march.

	Calories
Basal metabolism	1767
Effort of standing	118
Walking 10 hours, 3 miles per hour	1705
Carrying pack (44 lbs.) 20 kg	484
	4074

It seemed improbable that the soldier would require more.

The Division of Food and Nutrition, Medical Department, U. S. Army, was in command of Lt. Col. John R. Murlin from October 1, 1917, to December 1, 1918, and the following is a brief summary of the conclusions reached (R. J. Anderson[1]):

"No matter how carefully the food material is selected and the menus calculated, a successful diet can not be maintained unless provision is made for the proper preparation and cooking of the food. The finest raw material may be ruined by poor cooks . . . The number [of graduate cooks] who actually knew how to cook was unfortunately small."

After the raw recruits reached camp the average loss in weight during the first week was half a kilogram. At the end of the second week they were at a low ebb physically, the second typhoid injection had been given, they were not accustomed to the new life, were all tired of the unusual drill, and most of them more or less homesick. During the third week they gained 0.5 kg. over their original weight, they were nearly normal, improved in their mental attitude, and were taking more food.[2]

Murlin and Hildebrandt[3] make a report based on the average composition of 134,879 rations issued in 427 messes in different camps, that the food consumption per man per day was 3633 calories. In addition to this regular ration the soldier bought candy, soft drinks, cake, ice cream, and sandwiches to the average amount of 365 calories, making a total food consumption of 3998 calories. The average weight of the American soldier was 66.6 kg.

The following details of the ration per man per day are instructive:

	Supplied	Wasted		Consumed	
	Gm.	Gm.	Per Cent.	Cals.	Cals. in Per Cent.
Protein	131	9	7	122	14
Fat	134	11	8	123	31
Carbohydrate	516	31	6	485	55
Calories	3899	266	7	3633	100

Cost 44.06 cents; waste 3.2 cents.
Total waste 0.35 kg.; edible waste 0.15 kg.

There was a larger consumption of food in the winter than in the summer months, as appears in the following table:

[1] Anderson, R. J.: Am. J. Physiol., 1919, **49**, 523.
[2] Howe, P. E., Mason, C. C., and Dinsmore, S. C.: *Ibid.*, p. 557.
[3] Murlin, J. R., and Hildebrandt, F. M.: *Ibid.*, p. 531.

CONSUMPTION OF FOOD BY MONTHS

	Cals. per Man per Day		Cals. per Man per Day
Oct., 1917	3606	June, 1918	3517
Nov., "	3706	July, "	3609
Dec., "	3819	Aug., "	3658
Jan., 1918	3827	Sept., "	3487
Feb., "	3864	Oct., "	3727
Mar., "	3894	Nov., "	3918
Apr., "	3545	Dec., "	4145
May, "	3514		

Perhaps the cold air produces greater activity.

Murlin gives the following interesting comparison of measured standards determined under widely different conditions:

COMPARISON OF THE SOLDIER'S DIET IN THE UNITED STATES TRAINING CAMPS WITH OTHER STANDARD DIETS FOR HARD MUSCULAR WORK

(Percentages of calories in italics)

	Protein	Fat	Carbohydrate	Calories
	Gm.	Gm.	Gm.	
Sundström (Finnish peasant)	136	83	523	3474
	(16)	*(22)*	*(62)*	
Voit (hard labor)	145	100	500	3574
	(17)	*(26)*	*(57)*	
U. S. soldier (hard training)	129	136	545	3998
	(13)	*(32)*	*(56)*	
Atwater (farmer, hard labor)	150	125	580	4150
	(15)	*(28)*	*(57)*	

The Finnish peasant, the German laboring man, the American farmer at hard labor, the United States soldier at hard labor, divide their food so that of the total grams ingested in the diet there are 13 to 17 per cent. for protein, 22 to 32 per cent. for fat, and 56 to 62 per cent. for carbohydrate. The carbohydrate varies between 500 and 580 grams in these variously determined dietaries.

There was less protein and more fat taken by the American soldier than appears in the other dietaries given above. His diet contained about 30 per cent. of the calories in fat. According to Anderson[1] this figure was often 25 per cent., but rose to between 30 and 40 per cent. when fresh butter was supplied.

Hoskins[2] finds a large consumption of food in American military hospitals and reports the following irregularities in the day-to-day intake:

[1] Anderson, R. J.: Am. J. Physiol., 1919, **49**, 523.
[2] Hoskins, R. G.: *Ibid.*, p. 578.

	Calories per Man
Monday	3175
Tuesday	4258
Wednesday	3673
Thursday	4418
Friday	2855
Saturday	3690
Sunday	3420
Average	3638

The low figure on Friday is attributed to fish for dinner and supper, a commodity which was usually unpopular.

Investigations by Cathcart[1] into the energy requirement of a British soldier present the following very interesting results:

	Cals per Hr.		Cals. per Hr.
Lying, post-absorptive	67	Entrenching	331
" after meals	75	Assault	383
Standing at ease	76	Bayonet exercise	215
" " attention	90	Musketry	178
Sitting (lectures)	86	Anti-gas	145
Marching, drill order	319	Guard and sentry drill	181
" battle order	379	Field work	330
" full equipment	413	Fatigues	241
Route marching	457	Kit inspection	130
Company drill	228	Lewis gun	94

Cathcart also computes the weekly energy expenditure of adult recruits as follows:

WEEKLY ENERGY EXPENDITURE OF RECRUITS
(Average per day = 3574 calories)

	No. of Hours	Calories		
		Per Hour	Total	Per Cent.
Sleep	56	69	3854	15.4
Meals	21	108	2268	9.0
Cleaning	7	130	910	3.6
Fatigues	2	207	414	1.6
Free time:				
Resting	18	75	1350	5.6
Active	18	300	5400	21.6
Drill	46	235	10810	43.2

One-third of the time is spent in sleep at a cost of 15 per cent. of the total food fuel necessary. Twenty-seven per cent. of the day is absorbed in drill at a cost of 43.2 per cent. of the fuel. The food cost of the free time was about one-quarter the cost of the week's intake of food.

[1] Cathcart, E. P.: History of the Great War. Medical Services, Hygiene of the War, 1923, 2, 108.

Cathcart has also shown that to carry the 1914 leather equipment of the British soldier at the rate of 90 yards per minute required 4.25 calories of energy per minute, whereas the new modification in equipment required only 3.66 calories. If the equipment be carried 2 hours a day the saving would be 70.8 calories per man per day, 70,800 per battalion per day, and over a million calories, or the equivalent of about 1000 loaves of bread, for a division of 15,000 men. The subject of army nutrition has been well reviewed by Rockwood.[1]

DIET STATISTICS

The "standard" dietaries are given below, not because they are inflexible requirements in any sense of the word, but merely for the convenience of the reader. The individual standard will ever be controlled by climate, the amount and kind of mechanical effort; by appetite, purse and dietetic prejudice.

STANDARD DIETARIES FOR A MAN OF 70 KILOGRAMS

(Weights in grams)

	Voit	Rubner	Atwater
Light work:			
Protein	....	123	100
Fat	....	46	*
Carbohydrates	....	377	*
Calories	....	2445	2700
Medium work:			
Protein	118	127	125
Fat	56	52	*
Carbohydrates	500	509	*
Calories	3055	2868	3400
Hard work:			
Protein	145	165	150
Fat	100	70	*
Carbohydrates	500	565	*
Calories	3574	3362	4150

* Carbohydrates and fats to make up the fuel value.

Rubner[2] cites the following food values consumed daily per inhabitant of different cities, based upon municipal statistics of gross consumption:

MUNICIPAL FOOD STATISTICS

	Protein	Fat	Carbohydrates	Calories
	Grams	Grams	Grams	
Königsberg	84	31	414	2394
Munich	96	65	492	3014
Paris	98	64	465	2903
London	98	60	416	2665

[1] Rockwood, P. R.: Military Surgeon, 1925, **56**, 385.

[2] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, p. 160.

In contrast to this comparative uniformity, hospital dietaries, as regulated by the management of such institutions, vary greatly.

Rubner[1] cites the following hospital dietaries:

HOSPITAL DIETARIES

	Protein	Fat	Carbohydrates	Calories
	Grams	Grams	Grams	
Munich	92	54	157	1381
Augsburg	94	57	222	1823
Halle	92	30	393	2267
England	107	69	533	3266

An interesting study of the dietary of a poorhouse in Helsingfors, Finland, was made by Elizabeth Koch.[2] A total of 3355 calories was offered to each of five old men daily and 2430 were taken per person. Of the food offered, 1500 calories were contained in bread. The dietary was thus arranged:

Breakfast. Daily: 200 gm. potatoes; ½ liter skimmed milk; 40 gm. butter.
Four times a week, 50 gm. salt fish (Strömling); bread, 200 gm.
Dinner. Daily: 200 gm. bread.
Four times weekly, 100 gm. meat; 200 gm. potatoes.
Twice a week bean soup. Beets and barley also furnished.
Supper. Mostly bread, skimmed milk, and wheaten grits.

When taking this diet the inmates of the institution consumed an average of 106 grams of protein, 55 grams of fat, 361 grams of carbohydrates, and 34 grams of salts. The total quantity of milk offered, amounting to between 667 and 1000 c.c. daily per person, was in each case completely taken. Old men of seventy-five years took a fair quantity of food, as appears from the following analysis:

	Age	Weight	Height	Calories in Food	Calories per Kg.
	Years	Kg.	M.		
M	54	62.5	1.64	2307	36.9
J	60	72.5	1.76	2790	38.5
Mu	70	70.5	1.65	2565	36.4
A	75	65.0	1.64	2379	36.5
L	79	60.0	1.65	2108	35.1

The author concludes that the quantity of food needed by old men is slightly below the normal for young adults (see p. 139).

[1] Rubner, M.: *Loc. cit.*, p. 157.
[2] Koch, E.: Skan. Arch. Physiol., 1911, **25**, 315.

THE IMPORTANCE OF FLAVOR

The population of a city will ordinarily sustain itself in accordance with its needs. In public institutions, however, such as poorhouses, prisons, asylums, hospitals, and in military and naval establishments, scientific knowledge of the needs of the individual becomes a very important consideration. The prolonged endurance of an army of soldiers is just as dependent on an ample army ration as is the battleship dependent on its supply of fuel. Not only the quantity of the food makes for the well-being, but it must taste well. No amount of actual fuel value could compel the American soldiers of the Spanish-American war to eat the "embalmed beef" furnished by the Government. The flavor is to the man what oil is to the machinery of the battleship. Without flavor in the food the digestive apparatus does not run smoothly. From the ancient medical school at Salernum one hears "non e digestio sine caseo." In ordinary civilized life even psychical influences act. The cloth on the table must be spotless, and the environment inviting. Hawk[1] tells us that reading the newspaper at the table does not alter the digestion. He furthermore states that unappetizing food taken in unpleasant surroundings will be wholly digested provided it can be retained by the stomach.

In the process of manufacture of Liebig's extract of beef muscle creatin is largely converted into creatinin. Such an extract, which contains also xanthin, is not strictly a food, since its constituents are largely ready for elimination in the urine.[2] Bürgi[3] shows that if meat extract be administered it is excreted in the urine, excepting 4.57 per cent. of its nitrogen, 14.85 per cent. of its carbon, and 17.55 per cent. of its energy content.

Its value lies in its *flavor,* which promotes the proper flow of the digestive juices.[4] Habits of diet differ. Tastes are changeable. The Chinese serve a dinner of thirty-five courses. They may eat a rare delicacy, the edible bird's nest, believed to be largely derived from the mucin of the salivary glands of certain swifts which construct them in coves on the seashore.[5]

[1] Hawk, P. B. *et al.:* Am. J. Physiol., 1920, **52,** 1.
[2] Rubner, M.: Z. f. Biol., 1883, **19,** 343.
[3] Bürgi, E.: Arch. f. Hyg., 1904, **51,** 1.
[4] Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, 1881, **6,** Pt. 1, p. 449.
[5] Wang, C. C.: J. Biol. Chem., 1921, **49,** 429.

It may be incidentally remarked that the principal value of many "patent" foods, "invalid" foods, etc., lies in their flavor. If agreeable to the taste of the individual they usually afford a harmless indulgence. That beef, milk, cream, butter, and rice are quite as suitable for all the purposes of proper living is a fact not sufficiently advertised. The old-time fraud of "patent" foods being "brain restorers" is as foolish a lie as can be written.

BEHAVIOR OF VARIOUS INDIVIDUAL FOODS

One takes as food milk, eggs, various meats, such as beef, veal, pork, mutton, fish; also cereals, such as bread, rice, maize, macaroni, beans, and peas. Sometimes alcoholic beverages are added. The calorific values may be calculated by determining the composition of the various nutrient materials by analysis and by multiplying the number of grams of each constituent by the factor which represents its fuel value to the organism (see p. 42).

As a simple illustration of this the following experiment of Rubner[1] may be cited: A man weighing 46 kilograms ate nothing but eggs for two days—22 on the first day and 20 on the second. The 22 eggs contained 1017.4 grams of material; the 20 eggs, 878.8 grams, an average of 948.1 grams per day. Since 100 grams of egg contain 14.1 grams of protein and 10.9 grams of fat, 948.1 grams would contain a daily allowance of 133.6 grams of protein and 103 grams of fat. If Rubner's standard values for the energy content are used, the result will be as follows:

133.6 grams protein × 4.1 = 547 calories.
103.3 grams fat × 9.3 = 961 calories.

Total..... = 1508 calories,
or 33 calories per kilogram.

This dietary of eggs was, therefore, nearly sufficient for the fuel requirement of this undersized individual. Notwithstanding the large amount of protein in the dietary there was a loss of body protein equal to 7.5 grams per day.

The results of an exclusive milk diet are thus summarized by Rubner:[2] Milk (2438 grams), containing 84 grams of protein and two-thirds of the requirement of energy for the individual, produced a deposit of protein equal to 6.7 grams daily (p. 365). To cover a

[1] Rubner, M.: Z. f. Biol., 1879, **15**, 127.

[2] Rubner, M.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 1903, **1**, p. 132.

requirement of 2400 calories daily 3410 grams of milk would be needed, which contain 140 grams of protein. For a laboring man with a requirement of 3080 calories, 4380 grams of milk with 180 grams of protein would be necessary.

Thomas[1] drank 10.7 liters of whole milk (6781 calories) in one day, taking it up to the limit of his capacity. Of 53.3 grams of nitrogen in the milk, 28.7 grams appeared in the urine of the day and 21.1 grams were added to the body. Of 67.4 grams of salts contained in the milk, 36.9 grams were present in the urine of the twenty-four-hour period and 29.5 grams were passed in the feces attributable to the diet; the power to absorb such a diet was therefore great. Dried milk powder preparations were absorbed with as great ease as whole milk.

It is evident that milk with its high protein content is a food *par excellence* for the growing organism or for the invalid convalescing from wasting disease. It contains too large an amount of protein for a normal adult. A mixture of milk, toast, and cream (creamed milk-toast) may produce a modified milk diet of proper value and easy digestibility. In America the dish is known as "half and half," making a delicious and satisfying luncheon. It consists of half milk, half cream, with rolls and graham biscuits, the last for flavor. An exclusive milk diet contains too little iron for the needs of a normal adult.

Moritz[2] recommends milk alone in treatment of obesity, in quantities varying between 1.5 and 2.5 liters daily. The normal weight in kilograms of the individual is calculated from his height, and each kilogram of such weight is provided with 16 to 17 calories in the diet, an amount which is contained in 25 c.c. of milk. Should the normal weight be 80 kilograms, 2000 grams of milk are administered daily in five portions. Such treatment brings about a considerable loss in body weight, and, although some body nitrogen is lost, a state of weakness does not ensue.

Rubner finds that 1500 grams of good white bread containing 104.4 grams of protein will maintain a working man in nitrogenous and calorific equilibrium. (See page 55.)

Thomas[3] took on three successive days an average of 2760 grams of fresh bananas which were not completely ripe, and to this he

[1] Thomas, K.: Arch. f. Physiol., 1909, p. 417.
[2] Moritz, F.: Münchener med. Wochnschr., 1908, **55**, 1569.
[3] Thomas, K.: Arch. f. Physiol., 1910, Suppl., p. 29.

added 300 grams of sugar. This gave a total intake of 4.32 grams of nitrogen and 2741 calories daily. Although a preliminary diet of starch and sugar had reduced the urinary nitrogen to 3 grams at the beginning of the experiment, nitrogen equilibrium could not be obtained when the above noted amount of bananas was ingested. The unripened starch of the banana is eliminated in the feces. Ripe banana in which almost all the starch has been converted into glucose is very completely digestible. Whereas five parts of potato protein may replace four of body protein in establishing nitrogen equilibrium, the protein of banana is not so efficient. Yet in tropical countries, such as the sea-coast of East Africa, the Congo, and in the Pacific Islands, during the six months of the rainy season (in which the banana is ripe), it furnishes almost the exclusive diet of the natives. It is preferred to potatoes because it can be obtained almost without labor. Banana flour is also prepared in these localities by drying unripe bananas in the sun.

BEHAVOIR OF BEVERAGES

If water be taken when the stomach is empty it quickly passes through the pylorus into the intestine. Taken with food, however, its exit from the stomach is considerably delayed; the delay accounts for some of the pleasure of afternoon tea when taken with toast. Beer remains in the stomach longer than water, and this may be due to the extractive substances or to a narcotizing effect upon the musculature of the stomach.[1]

Atwater and Benedict[2] have conclusively shown that alcohol may be used in the economy in place of isodynamic quantities of carbohydrates and fats. The following table shows the average of experiments on a resting individual which lasted twenty-three days:

INFLUENCE OF ALCOHOL ON METABOLISM

	Duration in Days	In the Food in Grams			Alcohol Gm.	Cal. in Food	Cal. of Metabolism	Protein Balance
		Protein	Fat	Carbohydrates				
Ordinary diet	13	114	69	354	....	2496	2221	−2.0
Alcohol-containing diet	10	115	47	273	72.2	2488	2221	−3.8

[1] Gröbbels, F.: Z. physiol. Chem., 1914, **89**, 1.

[2] Atwater, W. O., and Benedict, F. G.: Mem. Nat. Acad. Sc., Washington, 1902, **8**, 231.

Atwater and Benedict employed diets containing about 2500 calories for a man at rest and 3500 for a man at work. During the alcohol days 500 of the calories were supplied in 72 grams of alcohol, or about what is contained in a bottle of claret. The metabolism of the individual as expressed in calories was unchanged by the substitution of alcohol in the diet. The alcohol was given in six small doses and 98 per cent. was burned by the organism.

On the ordinary diet 33.7 grams of fat were daily added to the body, and on the alcohol days 34.1 grams. These very valuable observations make it evident that alcohol is not a direct cause of obesity.

A liter of German beer contains 3 to 4 per cent. of alcohol and 5 to 6 per cent. extractives. It yields 450 calories to the body, only half being derived from alcohol, the rest from the dextrin and protein-like extractives. Here is a material whose "fattening" properties may be very highly considered.

It is reported that alcohol is present in normal human blood to the extent of 3 parts in 100,000. When alcohol is drunk it passes into the blood as such, and as much as 2 parts in 1000 has been found in the blood of a drunken man by Schweisheimer.[1] According to this author, the intensity of the drunkenness depends on the concentration of alcohol in the blood. A maximum concentration is reached about an hour and a half to two hours after drinking and may remain high for five hours. Those who are accustomed to alcohol oxidize it all in seven and a half hours, whereas those who have been abstainers require twice that time.

It is interesting that although alcohol ingestion reduces the respiratory quotient after it has been given, it has never been found to reduce it to such an extent as to indicate that it is the main source of the energy supply of the body.

An experiment by Durig[2] showed that after giving 30 grams of fructose to a man every hour the respiratory quotient rose to unity; but if 30 c.c. of alcohol were given about the same time the respiratory quotient was depressed to about 0.80. Alcohol was, therefore, in large measure oxidized instead of sugar, but the respiratory quotient did not approximate 0.67, the quotient for alcohol itself, as would have been the case if the source of energy had been exclusively

[1] Schweisheimer, W.: Deut. Arch. klin. Med., 1913, **109**, 271.
[2] Tögel, O., Brezina, E., and Durig, A.: "Biochem. Z., 1913, **50**, 298.

alcohol (see p. 386). These authors find no summation of dynamic effect when alcohol and carbohydrate are oxidized together (see p. 386).

Völtz and Dietrich[1] have given dogs 2 c.c. of alcohol per kilogram of body weight. After ten hours only 73 per cent. of the material had been oxidized, or enough to provide for 43 per cent. of the energy requirement of the time. About 90 per cent. was oxidized in fifteen hours, but it required about eighteen to twenty hours for the dog to rid himself of the material. Alcohol, therefore, is not a quickly oxidizable substance, but it remains in the blood a long time. Although sugar may entirely displace fat metabolism, alcohol can only in part displace carbohydrate from its part in metabolism.

All alcoholic beverages are taken with a twofold object: first, the desire for flavor, and second, for stimulation; their food value, as above described, is usually little considered. In general, it may be said that alcohol as a stomachic is valueless when the gastric juice is normal, but it is said to be beneficial in cases of supersecretion, hypochlorhydria, and loss of appetite. Under these circumstances small amounts of beverages containing 5 to 10 per cent. of alcohol are sufficient for all purposes.[2]

If alcoholic beverages are taken they should be an adjunct to the taking of ordinary foods. Southgate[3] administered 96 c.c. of absolute alcohol, diluted to make an 8 per cent. solution, to three persons in the morning both with and without food, and found that the alcohol content of the blood was much less when food was taken than without food. E. Mellanby[4] had previously shown this for a milk diet. Southgate's results are as follows:

	Cmm. Alcohol in 100 C.C. Blood		
	1 Hr.	2½ Hrs.	6½ Hrs.
Alcohol, 96 c.c.	152	150	83
Alcohol, 96 c.c.; milk, 530 c.c.; bread, 183 gm.	120	118	47

Taken in moderation alcoholic beverages contribute greatly to human happiness and constitute one of the solaces of mankind. Taken in excess they lead to many social evils. "Prohibition" as

[1] Völtz, W., and Dietrich, W.: Biochem. Z., 1915, **68**, 118.
[2] Zitowitsch, J. S.: Abstract in Biochem. Centralbl., 1905–06, **4**, 574.
[3] Southgate, H. W.: Biochem. J., 1925, **19**, 737.
[4] Mellanby, E.: British Med. Res. Com., Special Report Series No. 31, 1919.

currently practiced in the United States is not entirely a blessing. It is not morally wrong to drink a glass of wine and therefore it is not commonly accepted as a crime to do so.

The subject of alcohol could be spun out into a considerable story, but for further details the reader is referred to other sources.[1]

SALTS OF THE DIET

The ash constituents of a dietary are certainly of importance.[2] In fasting there is a constant loss of salts from the body. There is apparently a "wear-and-tear" metabolism of the bones (see p. 105) which must be replaced by ingested salts.

The minimum amount of calcium needed in the daily diet in order to establish "calcium equilibrium" is unknown. Benedict's fasting man eliminated 0.138 gram of calcium oxid in the urine of the thirty-first day of his fast.

From the work of Bertram,[3] it appears that a man can be maintained in calcium equilibrium when the diet contains 0.4 gram of calcium oxid. Herxheimer[4] obtained the same result when a man took 0.86 gram of calcium oxid.

German authorities state that a man requires about 1.5 grams of calcium oxid daily. Thus Hornemann[5] places the requirement of calcium oxid at 1.7 grams and of iron at 55 milligrams, the sodium chlorid balance being maintained with 5 grams of that salt daily, or half to one-quarter the amount usually taken.

Tigerstedt[6] reports that the diet of the Finns contains between 2 and 6 grams of calcium oxid daily, and this on account of the large intake of milk (see p. 462), which averages 1570 c.c. for men and 913 c.c. for women.

In contrast with this, the ordinary American diet of the average inhabitant of the Eastern States, as studied by Sherman, Mettler, and Sinclair[7] presents a sorry spectacle.

[1] "The Use of Alcohol in Medicine:" Benedict, F. G., Cushny, A. R., Meltzer, S. J., Lusk, G., Boston Med. and Surg. J., 1902, **147**, 31; "Bibliographie der gesamten wissenschaftlichen Literatur über den Alkohol und den Alkoholismus," Berlin and Vienna, 1904, by Emil Abderhalden.

[2] For the older literature see Albu, A., and Neuberg, K.: "Physiologie und Pathologie des Mineralstoffwechsels," Berlin, 1906.

[3] Bertram, J.: Z. f. Biol., 1878, **14**, 354.

[4] Herxheimer, G.: Berliner klin. Wchnschr., 1897, **34**, 423.

[5] Hornemann, O.: Z. f. Hyg., 1913, **75**, 553.

[6] Tigerstedt, R.: Skan. Arch. Physiol., 1911, **24**, 97.

[7] Sherman, H. C., Mettler, A. J., and Sinclair, J. E.: U. S. Dept. of Agriculture, Office of Experiment Stations, 1910, Bulletin 227. Table giving the ash constituents of the edible portions of various food materials is given in this bulletin on p. 41.

The salt content of the dietaries taken by the people of the two nations may be thus contrasted:

ASH CONTENT OF ORDINARY DIETARIES, WEIGHTS IN GRAMS

Calories in Diet	Finnish			American		
	P_2O_5	CaO	MgO	P_2O_5	CaO	MgO
Over 4000	10.86	6.10	2.02	4.24	0.79	0.89
4000–3500	9.46	3.79	1.85	3.22	0.94	0.51
3500–3000	8.18	4.02	1.53	3.29	0.99	0.50
3000–2500	6.93	3.51	1.23	3.20	0.92	0.46
2500–2000	5.64	2.96	1.03	2.06	0.36	0.32
2000–1500	5.12	2.85	0.78	1.84	0.68	0.23

Tigerstedt points out that this difference in the salt intake of the different peoples is due to the fact that the American subjects took an average of only 250 c.c. of milk in their diets daily. As pointed out by Sherman, the American family has only to drink more milk or eat more cheese in order to raise the ash content of the dietary. Those in charge of the food supply of institutions should not forget the importance of milk, and every care should be exercised to prevent the cost of good milk from becoming prohibitive.

Sherman and his school have continued unceasingly to advocate a proper intake of calcium in the dietary. Sherman, Rose, and Rose[1] found that the usual American dietary contained only 0.45 gm. Ca and that 1 gm., or the quantity contained in a liter of milk, was really required. Sherman and Hawley[2] state that 750 c.c. of milk are insufficient to give a maximum storage of Ca daily and that such storage increases when 1000 gm. of milk are given. Also, they report that the Ca of vegetables is not so efficiently utilized as that of milk, and they commend a quart of milk a day as advisable for each member of the family.

Blatherwick and Long,[3] confirming M. S. Rose,[4] find that the calcium of carrots is well utilized by man, and they find this is generally true as regards the calcium and phosphorus of lettuce, asparagus, celery, spinach, summer squash, and cabbage.

Wha[5] states that the calcium of milk is combined with milk colloids but that acid ionizes all of it. All the potassium and chlorin of

[1] Sherman, H. C., Rose, A. R., and Rose, M. S.: J. Biol. Chem., 1920, **44**, 21.
[2] Sherman, H. C., and Hawley, E.: *Ibid.*, 1922, **53**, 375.
[3] Blatherwick, N. R., and Long, M. L.: *Ibid.*, 1922, **52**, 125.
[4] Rose, M. S.: *Ibid.*, 1920, **41**, 349.
[5] Wha, C.: Biochem. Z., 1924, **144**, 278.

the milk is diffusible, but 60 per cent. of the phosphoric acid is not diffusible.

Osborne and Mendel[1] showed that the growing animal can fully supply its salt requirements from inorganic sources and emphasized anew that it is unnecessary to consider the presence of Ca, P, and Fe in the natural foods to the degree currently believed. Later Steenbock, Hart, Sell, and Jones[2] found that in the growth of young rats the Ca supply could be furnished with equal availability by calcium lactate, carbonate, phosphate, silicate, or sulphate, when these were given in liberal amounts.

As regards *phosphorus* Sherman[3] judges from the general average of all the data that 0.88 gm. of P are required daily for a body weight of 70 kg. He states that only 8 out of 224 American families received this amount in their daily diet.

Miller[4] states of *potassium* that young rats grow properly if they have 0.1 per cent. in their dietary. Whenever less is given an inadequate supply of this element may not only prevent tissue growth but cause abnormal changes, such as edematous eyes and respiratory trouble. Miller also takes issue with Bunge[5] and does not believe that the ingestion of potassium salts will cause the elimination of sodium chlorid to the detriment of the body. Bunge had said man put salt on potato, which is rich in potassium, to prevent the detrimental removal of sodium chlorid from the body.

Briggs[6] analyzed the bloods of 50 different patients in a variety of diseases and, except in nephritis, found the values for Na, K, Ca, Mg, Cl, and P to be entirely normal. He concludes that marked variations of the inorganic constituents of the blood are quite exceptional.[7]

The American families were reported to consume between 35 and 7 milligrams of iron daily, the amount ingested running almost parallel with the intake of protein in the food. This is much less than the minimum called for by Hornemann.

[1] Osborne, T. B., and Mendel, L. B., with E. L. Ferry and A. J. Wakeman: J. Biol. Chem., 1918, **34**, 131.
[2] Steenbock, H., Hart, E. B., Sell, M. T., and Jones, J. H.: *Ibid.*, 1923, **56**, 375.
[3] Sherman, H. C., Rose, A. R., Koch, M., Mathews, E., and Osterberg, E.: *Ibid.*, 1920, **41**, 173.
[4] Miller, H. G.: *Ibid.*, 1923, **55**, 61; 1926, **67**, 71.
[5] Bunge, G.: Z. f. Biol. 1873, **9**, 104.
[6] Briggs, A. P.: J. Biol. Chem., 1923, **57**, 351.
[7] For a brilliant treatise on "The Paleochemistry of the Body Fluids and Tissues" read Macallum, A. B.: Physiol. Rev., 1926, **6**, 316.

The requirement of iron per day is given by Sherman as 15 mg. Hart[1] and his collaborators, confirming older work of Abderhalden,[2] show that in spite of the addition of inorganic iron to a milk diet given to rabbits, the animals become anemic. The anemia could be prevented by giving fresh cabbage or an extract of desiccated cabbage or of maize meal prepared by extracting these by the means of cold alcohol. The extract is practically free from iron. Since the nutritional anemia can also be cured by the ash of lettuce or the ash of cabbage, the authors conclude that the deficiency in milk is essentially of inorganic character. They are not sure whether or not the curative factor lies in the iron content of the ash and are continuing the experiment.

There was much information in the older literature which pointed to the liver as a predominant storehouse of organic iron in the form of ferratin, as it was called.[3]

Liver and extracts of liver have recently been used in the successful treatment of pernicious anemia by Minot and Murphy.[4]

The table on p. 485, compiled from part of the data presented by Sherman[5] and by Sherman and Gettler,[6] gives the ash content of various edible foods.

Meat, eggs, oatmeal, unmilled wheat, and green vegetables contain much iron. Milk, polished rice, and white flour contain little iron. Milk, oatmeal, and dried beans furnish large amounts of calcium.

Not only is the quantity of the ash constituents of significance, but Sherman and Gettler[7] have shown the importance of the acid or base-forming potency of the ash of different foods. Thus, a dietary which contained 3000 calories, 300 calories being in potato, was given to a man, and then the potato was replaced by rice containing 300 calories. The result of the change was an increase of 50 per cent. in the titratible acidity of the urine and an increase in the amount of ammonia excreted.

[1] Hart, E. B., Elvehjem, C. A., Waddell, J., and Herrin, R. C.: J. Biol. Chem., 1927, **72**, 299.

[2] Abderhalden, E. (cand. med.): Z. f. Biol., 1900, **39**, 193.

[3] Marfori, P.: Arch. exper. Path. u. Phar., 1891–92, **29**, 212; Schmiedeberg, O.: *Ibid.*, 1893–94, **33**, 101. For this older literature see Lusk, G.: in Howell's "American Text-book of Physiology," 1900, **1**, p. 528.

[4] Minot, G. R., and Murphy, W. P.: J. Am. Med. Assn., 1926, **87**, 470.

[5] Sherman, H. C.: "Chemistry of Food and Nutrition," New York, 3d ed., 1927.

[6] Sherman, H. C., and Gettler, A. O.: J. Biol. Chem., 1912, **11**, 323.

[7] Sherman, H. C., and Gettler, A. O.: *Ibid.*

ASH CONTENT OF THE EDIBLE PORTION OF SOME COMMON FOODS

	In 100 Grams Fresh Substance						
	Iron	Calcium	Magnesium	Sodium	Potassium	Phosphorus	Chlorin
	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
Beefsteak, lean	3.8	8	24	67	35	22	50
Eggs	3.0	67	9	15	14	16	100
Milk, whole	0.2	120	11	51	142	94	120
Cornmeal	1.1						
Oatmeal	3.7	93	127	81	380	380	35
Rice, polished	0.7	8	27	21	68	89	50
Wheat flour	1.5	26	30	69	146	86	76
Wheat, entire grain	5.2	44	170	106	515	469	88
Beans, lima, dried	7.2	71	187	245	1743	336	25
Beans, string, fresh	1.6						
Cabbage	0.9	49	14	20	243	27	13
Corn, sweet	0.8						
Peas, dried	5.6	100	145	118	880	397	40
Potatoes	1.2	11	22	19	440	61	30
Spinach	3.8						
Turnips	0.6	64	169	59	332	51	40
Apples	0.3	10	8	15	124	13	4
Raisins	3.6	57	9	141	830	126	70

Blatherwick[1] has continued investigations along these lines, which show that foods which have a preponderance of base-forming elements lead to the formation of a urine less acid than the normal. Such foods are potatoes, oranges, raisins, apples, and bananas, and these are very efficient in reducing the acid output. Tomatoes are less valuable in this respect. Rice and whole wheat bread increase urinary acidity. Plums, prunes, and cranberries, through their content of benzoic acid, increase the urinary acidity. Blatherwick notes that the hydrogen ion concentration of thirty urines obtained from vegetarians was pH 6.64, in contrast with a value of pH 5.98 reported by Henderson and Palmer for the urines of persons living on a mixed diet, and he emphasizes the close relationship between the hydrogen ion concentration of the urine and its solvent power over uric acid. These findings are, therefore, in accord with those of Hindhede (p. 453) and should establish the potato upon a high plane of dietary dignity.

"War edema" occurred in Germany between January and April, 1917, at a time when there were no potatoes but plenty of turnips

[1] Blatherwick, N. R.: Arch. Int. Med., 1914, **14**, 409.

and an average protein intake of 40.5 gm. Jansen[1] stated that low protein intake was not the cause, but that the reason lay in a general injury of the tissues through malnutrition. There was an abnormally large intake of water and common salt, the retention of part of which produced the edema in an organism susceptible to it. Therapeutic treatment by addition of fat or carbohydrate to the diet brought about protein retention when the diet contained 15 gm. of nitrogen and in one case resulted in a loss of sodium chlorid from the body for 6 days at an average rate of 22 gm. per day. The primary difficulty may have been in the difference in the supply of salts in the potato and in the turnip when administered under conditions of caloric insufficiency of diet.

Exact and detailed information regarding the mineral elements in the diet is to be found in H. C. Sherman's "Chemistry of Food and Nutrition," New York, 3d ed., 1927, and to this the reader is referred for further information.

[1] Jansen, W. H.: Deut. Arch. klin. Med., 1920, **131**, 144–200; 330–370.

CHAPTER XIX

THE NUTRITIVE VALUE OF VARIOUS MATERIALS USED AS FOODS

La diversité et la multiplicité des aliments est une règle d' hygiène très importante.—MAGENDIE, 1836.

IN 1897 Eijkman[1] published the observation that the disease beriberi was due to a one-sided diet of polished rice, and that if rice were not milled, but eaten with its pericarp, beriberi did not ensue. Eijkman[2] also made the very valuable discovery that pigeons, when fed with polished rice, developed a polyneuritis analogous to that found in human beriberi, and that the addition of rice bran (rice polishings) to the diet prevented this condition.[3]

About this same time Röhmann[4] found that if, instead of natural foods, purified materials, such as casein, egg-albumin, vitellin, potato starch, wheat starch, and oleomargarin, together with the proper salts, were mixed and given to mice, their offspring were difficult to rear with this food and that no living young could be obtained from them.[5] These experiments appeared difficult of interpretation.

In reality, the work of Eijkman and of Röhmann was the beginning of a scientific knowledge of the so-called "deficiency diseases." It now appears that a proper diet for growth or maintenance must contain not only protein, fat, carbohydrate, and salts, but also some substances existing in natural foods, in very minute quantities, which are absolutely essential to the harmonious fulfilment of the life processes.

Van Leersum calls attention to the little known communication of C. A. Pekelharing[6] which was published in Dutch in 1905 and which reads as follows:

"When white mice are fed on bread baked with casein, albumin, rice-flour, lard and a mixture of all the salts which ought to be found

[1] Eijkman, C.: Virchow's Arch. path. Anat., 1897, **149**, 187.
[2] Eijkman, C.: *Ibid.*, 1897, **148**, 523.
[3] For useful reference consult Vedder, E. B.: "Beriberi," New York, 1913.
[4] Röhmann, F.: Klin. therap. Wchnschr., 1902, **9**, 1306.
[5] Consult Osborne, T., and Mendel, L. B.: Carnegie Institution of Washington, Pub. 156, 1911; Röhmann, F.: "Ueber künstliche Ernährung und Vitamine," Berlin, 1916.
[6] Pekelharing, C. A.: Nederlandsch Tijdschrift voor Geneeskunde, 1905, **2**, p. 111.

in their food, while they are only given water to drink, the animals starve to death. During the first few days all is well. The bread is eagerly nibbled and the mice look healthy. But soon they get thinner, their appetite diminishes and in four weeks all the animals are dead. If, however, instead of water they are given milk to drink, they keep in good health, though the quantity of albumin, lactose and fat which they assimilate with the milk is quite negligible in comparison with what the bread on which they are fed contains. The element in the milk which keeps the animals alive also occurs in the whey from which casein and fat have been eliminated. Till now my efforts constantly repeated during the last few years, to separate this substance from the whey and get to know more about it, have not led to a satisfactory result, so I shall not say any more about them. My intention is only to point out that there is a still unknown substance in milk, which, even in very small quantities, is of paramount importance to nutrition. If this substance is absent, the organism loses the power properly to assimilate the well-known principal parts of food, the appetite is lost and with apparent abundance the animals die of want. Undoubtedly this substance not only occurs in milk but in all sorts of foodstuffs, both of vegetable and animal origin."

Another pioneer in this field was Gowland Hopkins,[1] who wrote in 1906, "No animal can live on a mixture of pure protein, fat, and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal is adjusted to live either on plant tissues or the tissues of other animals, and these contain countless substances other than proteins, carbohydrates, and fats . . . In diseases such as rickets and, particularly, in scurvy we have had for long years knowledge of a dietetic factor but though we know how to benefit these conditions empirically, the real errors in the diet are to this day quite obscure . . . Scurvy and rickets are conditions so severe that they force themselves on our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors."

The study of the "accessory factors" of diet, a term used by Hopkins, has been in the hands and heads of some of the ablest physiologic chemists during the past ten years, and it is extremely

[1] Hopkins, F. G.: "Analyst," 1906, **31**, 391.

difficult, perhaps impossible, to write of the subject and do even-handed justice toward the various contributors in the field. Hofmeister defines the unknown but beneficent factors alluded to here as "accessory food-stuffs," and Funk has called them "vitamins."[1] Objection is made to the term "accessory" on the ground that it implies something non-essential, and to the term "vitamin" on the ground that there is no evidence that the substance or substances in question are amins, nor that they are more valuable to life than other substances—epinephrin, for example. In acknowledgment of this insufficiency of information, McCollum[2] suggested the provisional use of two terms, the "fat-soluble A" and the "water-soluble B," as representing the factors necessary for adequate growth. The "water soluble B" cures beriberi and is regarded as identical with Funk's 'vitamins."

This terminology has since been extended to include vitamin C, the antiscorbutic vitamin, vitamin D, the antirachitic vitamin, and vitamin E, the fertility vitamin.

For the sake of simplicity, the word "vitamin" is now commonly used to express the group of as yet unidentified substances which at present cannot be classified with the familiar nutrients, proteins, fats, carbohydrates, inorganic salts, and water, but upon which the harmonious behavior of the organism depends and which are ordinarily ingested in traces in the food. The term "food hormone" is probably a more rational expression of what the vitamins signify (see p. 522).

It would be a useless and a thankless task to record here the great mass of literature which has filled our scientific journals on the subject of the vitamins, for this is already at hand in McCollum's "The Newer Knowledge of Nutrition."[3] The briefest outline must here suffice.

Interwoven with the experimental work upon the subject of the vitamins has been work upon the relative value of different proteins in nutrition. A diet may yield sufficient energy to maintain the organism and yet be a deficient dietary in that it lacks vitamins or contains insufficient salts or too little protein or protein of low nutritive value.

[1] Funk, C.: Ergeb. d. Physiol., 1913, **13**, 126.
[2] McCollum, E. V., Simmonds, N., and Pitz, W.: J. Biol. Chem., 1916, **25**, 105.
[3] McCollum, E. V., and Simmonds, N.: "The Newer Knowledge of Nutrition," 3d ed., New York, 1925.

VITAMIN A

Stepp[1] showed that when mice were fed with bread baked with a little milk this formed a complete diet, but if this diet were first extracted with alcohol and ether the animals all died. He[2] further reported that the addition of salts or fat or lecithin or cholesterol to the extracted bread was without beneficial influence when it was given to mice. However, the addition of ether-alcohol extracts from skimmed milk, from egg-yolk, or from calves' brains to bread which had been extracted furnished a diet capable of supporting mice. In a later paper Stepp[3] reported that ether extraction fails to remove the accessory substance necessary to life, whereas alcohol accomplishes this result; he therefore concludes that the significant substance is not a fat.

Experiments concerning growth may be conducted with especial ease upon hogs and rats. McCollum[4] concludes that the growth impulse of the hog is greater than that of the rat on account of the data contained in the following table:

	At Birth		Age = 280 Days		Weight at 280 Days / Weight at Birth	
	Weight, Grams	Body N, Grams	Weight, Grams	Body N, Grams	Body Weight	Body N
Rat	4.83	0.064	280	8.5	55	133
Hog	906	11.9	136,000	2407	150	202

It is evident that the hog, both as regards body weight and nitrogen content, increases relatively somewhat more rapidly than does the rat. However, in both species the growth impulse is very great and very constant, so that deviations in the curve of normal growth when caused by insufficiency of diet, may be readily established. The rat reaches full growth after two hundred and eighty days and lives about three years.

In 1911 Osborne and Mendel[5] published the first results of a prolonged series of valuable contributions to the knowledge of growth. These authors found that if a single protein, like casein, were added to a diet made up of starch, lard, agar, and "protein-free milk," such a diet became adequate for the growth of rats during the first two months of their lives. This is because it contains "water-

[1] Stepp, W.: Biochem. Z., 1909, **22,** 452.
[2] Stepp, W.: Z. f. Biol., 1911–12, **57,** 135.
[3] Stepp, W.: *Ibid.*, 1913, **62,** 405.
[4] McCollum, E. V., J. Biol. Chem., 1914, **19,** 323.
[5] Osborne, T., and Mendel, L. B.: "Feeding Experiments with Isolated Food-substances, Parts I and II," Carnegie Institution of Washington, Pub. 156, 1911.

soluble" vitamin B. The "protein-free milk" contains 0.7 per cent. of nitrogen, 80 per cent. of lactose, and 15 per cent. of inorganic salts, and Osborne and Mendel[1] estimate that 2.2 per cent. of milk protein is present. This makes 0.6 per cent. of the weight of the whole diet, or 3 per cent. of the total quantity of protein ingested when an isolated protein, like casein, is added to the food in such measure as to make the diet contain 18 per cent. of casein. In later work Osborne and Mendel state that the "protein-free milk" introduces protein only to the extent of 0.13 per cent. of the food given.

Hopkins[2] showed that a synthetic food, consisting of protein, carbohydrate, lard, and the proper salts, became an entirely satisfactory diet for growing rats if only 2 c.c. of milk were given also. The milk was administered before the rest of the diet in order to prove that it was not a lack of palatability in the synthetic food which was the cause of the failure of the rats to grow. Hopkins also made the very significant discovery that an alcoholic extract of milk solids or of yeast, when added to the synthetic diet "in astonishingly small amounts," caused normal growth. Though the synthetic diet contained plenty of calories (see p. 567) growth took place only when the accessory substances were administered.

McCollum and Davis[3] reported that, although young rats grew for sixty or ninety days on such diets as have been described, yet after this time growth suddenly stopped. It could be re-established if butter fat or the ether extract of egg-yolk was added to the diet. Apparently, the organism runs out of some organic complex which is indispensable to normal growth and without which maintenance in good condition is impossible.

Osborne and Mendel[4] independently reached the same results. There was a primary growth when a synthetic diet which included lard and "protein-free milk" was given, followed by failure to grow. If the lard were replaced by butter or egg-yolk or cod-liver oil, growth was resumed, but almond oil was inefficient in this regard. In connection with the high efficacy of cod-liver oil in promoting growth, Osborne and Mendel refer to its "popular yet inexplicable reputation for unique nutritive potency." Beef fat was found to be more valuable than lard.

[1] Osborne, T. B., and Mendel, L. B.: Z. physiol. Chem., 1912, **80,** 316.
[2] Hopkins, F. G.: J. Physiol., 1912, **44,** 425; Biochem. J., 1920, **14,** 721.
[3] McCollum, E. V., and Davis, M.: J. Biol. Chem., 1913, **15,** 167.
[4] Osborne, T. B., and Mendel, L. B.: *Ibid.*, 1913, **15,** 311; **16,** 423; 1914, **17,** 401.

McCollum and Davis[1] showed that olive oil and cotton-seed oil, like almond oil and lard, cannot be used to foster growth, whereas the fat of cod testicle and hog's kidney are very efficient. Curiously enough, the fat of the hog's heart is not of value in producing growth. Animal fats and especially milk fats have, therefore, nutrient virtues not expressed in calories.

Osborne and Mendel[2] noted that the rats which declined when the fat of the diet was lard or vegetable fat frequently developed *xerophthalmia*, an inflammation of the eye. This was cured by administering butter fat or cod oil. Lard is poor in vitamin A because a hog's diet contains little of it and because in the manufacture of lard it is exposed to oxygen at high temperatures. A grass fed hog however can store vitamin A.[3]

Xerophthalmia occurred among the children of Denmark during the war because the Danes sold butter to Germany and gave their own children skimmed milk filled with cocoanut butter, which is devoid of vitamin A. This was cured by rationing whole milk among the children.[4] The same trouble occurred in 1920 among adults in Danish institutions for the mentally deficient because the patients received milk skimmed by machinery, very few green vegetables, and no butter at all.

Steenbock, Nelson, and Hart[5] state that five dogs within a period of 94 days developed xerophthalmia when they were given a diet poor in vitamin A, thus placing dogs in the same category previously established for rats, mice, rabbits, chickens, and man. Cod oil cured the difficulty. Vitamins A and C are not necessary for the fertile egg production, growth, and maintenance of the common pigeon,[6] although vitamin B is necessary.

It was first shown by Hopkins[7] that when young were nursed by females receiving a diet deficient in vitamin A they grew to about one-half their normal size and showed many signs of undernutrition. This principle has been confirmed by others.[8] Sherman and Cam-

[1] McCollum, E. V., and Davis, M.: J. Biol. Chem., 1914, **19,** 245; 1915, **20,** 641; **21,** 179.

[2] Osborne, T. B., and Mendel, L. B.: J. Am. Med. Assn., 1921, **76,** 905.

[3] Drummond, J. C., Golding, J., Zilva, S. S., and Coward, K. H.: Biochem. J., 1920, **14,** 742.

[4] Bloch, C. E.: J. Hygiene, 1921, **19,** 283.

[5] Steenbock, H., Nelson, E. M., and Hart, E. B.: Am. J. Physiol., 1921–22, **58,** 14.

[6] Sugiura, K., and Benedict, S. R.: J. Biol. Chem., 1923, **55,** 33; Emmett, A. D., and Peacock, G.: *Ibid.*, 1923, **56,** 679.

[7] Hopkins, F. G.: Med. Research Com. Report, 1919, No. 38, p. 17.

[8] Steenbock, H., Sell, M. T., and Nelson, E. M.: J. Biol. Chem., 1923, **56,** 327; Korenchevsky, V., and M. Carr: Biochem. J., 1924, **18,** 1313.

mack[1] fed rats with diets graded in their content of vitamin A by giving different doses of the highly potent cod-liver oil, and found that the richer the diet was in this source of vitamin the more of it was stored in the body. For on withdrawal of the supply of vitamin A those rats which had received the largest quantity in the previous dietary survived the longest.

The supply of vitamin A originates chiefly from the green things of the field and of the sea. Marine diatoms and marine and fresh water algae have extraordinary potency as regards the synthetic production of the vitamin A factor, and these forms of life constitute the fundamental food supply of all marine animals.[2]

Whatever the reason, in plant structures the leaves are the richest in vitamin A, the roots next in order, and last of all the grains; sweet potatoes are quite potent,[3] also yellow corn,[4] although whole wheat, white corn, and oats contain very little. Dried yeast contains only 3 per cent. of fat, but this holds vitamin A.[5]

Cooper[6] reports that when a diet rich in vitamin A—butter, eggs, and cod-liver oil—is given to dogs or man, the alcohol ether extracts of both urine and gastric juice contain the vitamin.

Chemical Behavior.—Hopkins[7] has shown that vitamin A manifests marked resistance to heat alone at a temperature of 120° C., but is readily destroyed by simultaneous aeration of the fat, presumably because it is a substance prone to oxidation by atmospheric oxygen.

Aerated cod-liver oil will still cure rickets and promote growth, hence vitamin A is not the antirachitic vitamin D.[8] In the absence of vitamin A in the diet of children calcium deposits are normal and neither rickets nor osteoporosis develops.[9] Radiant energy of the sun will not prevent xerophthalmia as it will prevent rickets, though it delays its onset, possibly by raising the level of cellular activity of the organism to a point where the onslaughts of the disease are held in check for a time.[10]

[1] Sherman, H. C., and Cammack, M. L.: J. Biol. Chem., 1926, **68**, 69.

[2] Jameson, H. L., Drummond, J. C., and Coward, K. H.: Biochem. J., 1922, **16**, 482; Drummond, J. C., Zilva, S. S., and Coward, K. H.: *Ibid.*, p. 518; Coward, K. H.: *Ibid.*, 1925, **19**, 240.

[3] Steenbock, H., and Gross, E. G.: J. Biol. Chem., 1919, **40**, 501; Steenbock, H., and Gross, E. G., with Sell, M. T.: *Ibid.*, 1920, **41**, 149.

[4] Steenbock, H., and Coward, K. H.: *Ibid.*, 1927, **72**, 765.

[5] Luce, E. M., and Smedley-Maclean, I.: Biochem. J., 1925, **19**, 47.

[6] Cooper, E.: Am. J. Physiol., 1923–24, **67**, 454.

[7] Hopkins, F. G.: Biochem. J., 1920, **14**, 725.

[8] Steenbock, H., and Nelson, E. M.: J. Biol. Chem., 1923, **56**, 355.

[9] Bloch, C. E.: Am. J. Dis. Child., 1924, **28**, 659.

[10] Powers, G. F., Park, E. A., and Simmonds, N.: J. Biol. Chem., 1923, **55**, 575.

Cod-liver oil loses a considerable part of its original vitamin A potency in storage under conditions that permit oxidative changes, but emulsification in the absence of oxygen has no deleterious action on it.[1] After 9 years of cold storage 0.25 gm. of egg yolk per day cured xerophthalmia in rats quite as quickly as fresh eggs would have done.

Fridericia[2] has shown that, although rats grow normally when their diet contains either 10 or 20 per cent. of butter fat and not at all when 10 per cent. of hydrogenated whale oil is given instead of butter fat, yet when hydrogenated whale oil, 10 per cent., plus butter fat, 10 per cent., is administered, growth is much less than normal. Hydrogenated cocoanut oil or hydrogenated linseed oil do not have this inactivating effect, and the conclusion is drawn that peroxides in hydrogenated whale oil may destroy vitamin A of butter fat.

Osborne and Mendel[3] have discovered that a diet containing protein 90 per cent., salts 5 per cent., to which was added alfalfa for vitamin A and yeast for vitamin B, induces splendid growth in rats. Hence true fats are not essential for growth.

Finally, Drummond, Channon, and Coward[4] have completely separated cholesterol from vitamin A, they have distilled the cholesterol-free residue at 180 to 220° C. *in vacuo*, and have found active vitamin A in the distillate. The growth promoting dose of this material is 0.05 mg. per day for a rat. They state that their preparations are highly impure but are not toxic, as was the highly active biosterin of Takahashi.[5] They feel that the vitamin may be an unsaturated alcohol, but are not certain.

VITAMIN B

When a synthetic diet of food-stuffs, such as casein, starch, butter fats, water, and salts, is given to rats they fail to grow, lose their appetite, and eventually die. When a small amount of yeast is added the animals develop normally. Yeast contains vitamin B.[6] In the absence of this vitamin polyneuritis develops, as has already been described.

[1] Drummond, J. C., Zilva, S. S., and Coward, K. H.: J. Soc. Chem. Industry, 1924, **43**, 236 T.

[2] Fridericia, L. S.: J. Biol. Chem., 1923–25, **62**, 471.

[3] Osborne, T. B. and Mendel, L. B.: *Ibid.*, 1920–21, **45**, 145.

[4] Drummond, J. C., Channon, H. J., and Coward, K. H.: Biochem. J., 1925, **19**, 1047.

[5] Takahashi, K.: J. Chem. Soc., Japan, 1922, **43**, 828; see Hemano, S.: Biochem. Z., 1925, **163**, 438.

[6] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1917, **31**, 149.

As previously stated, Hopkins found that 2 c.c. of milk daily furnishes an adequate supply of vitamins for the proper growth of rats. Osborne and Mendel[1] find that 10 c.c. of cow's milk or 5 c.c. of human milk are necessary to supply vitamin B. If less than this is given yeast must be added. The reason for the lack of accord between the two authorities is not apparent.

It is evident, however, that the ingestion of a small quantity of milk daily is a satisfactory source of both vitamin A and vitamin B.

Voegtlin and Lake[2] state that if lean beef, which has been heated for 3 hours at 120° C. in the presence of sodium bicarbonate, be fed to cats, they develop symptoms of polyneuritis in 18 days, whereas dogs require a month or 6 weeks to show the symptoms. In man, living on milled rice, at least 87 days are required to produce beriberi.[3]

Carrots contain vitamin B, and in Japan it is proverbial that two carrots given to a horse before a race add to his speed.[4] Osborne and Mendel[5] find that spinach, cabbage, and other green foods, as well as the fresh juices of orange, lemon, and grape fruit, all contain vitamin B. Only small amounts are found in apples and pears, although prunes are quite a rich source of the vitamin.

Thus Bacharach[6] finds that young rats cease to grow after the omission for 7 days of orange juice from a diet whose other components are casein, rice starch, butter fat, and salt mixture. All the evidence points to little ability on the part of the rat to store vitamin B.[7] A previous surfeit of vitamin B in the diet does not prolong the life of the rat deprived of it. In the liver tissue, where it is ordinarily found in abundance, the supply becomes largely depleted.[8]

Beer is free from vitamins B and C. When India Pale Ale was given to rats as a substitute for vitamin B they developed polyneuritis. Given to monkeys, the animals developed scurvy.[9]

[1] Osborne, T. B., and Mendel, L. B., with Ferry, E. L., and Wakeman, A. J.: J. Biol. Chem., 1918, **34**, 537; Osborne, T. B., and Mendel, L. B., with Cannon, H. C.: Biochem. J., 1922, **16**, 363.

[2] Voegtlin, C., and Lake, G. C.: Am. J. Physiol., 1918–19, **47**, 558.

[3] Fraser, H., and Stanton, A. T.: Lancet, 1909, p. 451.

[4] Sugiura, K.: J. Biol. Chem., 1918, **36**, 191.

[5] Osborne, T. B., and Mendel, L. B., with Ferry, E. L., and Wakeman, A. J.: *Ibid.*, 1919, **37**, 187; Osborne, T. B. and Mendel, L. B., with Wakeman, A. J.: *Ibid.*, 1920, **42**, 465.

[6] Bacharach, A. L.: Biochem. J., 1925, **19**, 638.

[7] Steenbock, H., Sell, M. T., and Jones, J. H.: J. Biol. Chem., 1923, **55**, 411.

[8] Osborne, T. B., and Mendel, L. B., with Cannon, H. C.: *Ibid.*, 1923–24, **58**, 363.

[9] Harden, A., and Zilva, S. S.: Biochem. J., 1924, **18**, 1129.

As bread is the mainstay of mankind, its vitamin content is important. Magendie[1] noted that if a dog received white bread it lived 50 days, but when it received dark "soldier bread" it remained in perfect health. Bell and Mendel[2] report that there is no vitamin in white flour and that entire wheat is a relatively poor source of vitamin B.

Hartwell[3] has given white homemade bread with butter and salt mixture to rats and has obtained slow but continuous growth, and also reproduction. In a second series white and brown bread were compared. Female rats grew equally with either kind of bread, the males more rapidly on brown than on white bread. The difference in the diet had no influence upon gestation or lactation. With both diets litters were poor at birth and few of the offspring were weaned. The yeast used in bread making furnished ample vitamin B and the limiting factor was attributed to protein deficiency. The author truly says,

"A number of people *assume* that brown bread has a far greater dietetic value than white bread, but there are very few experimental data to warrant such an assumption . . . From a common sense point of view, also, it seems ridiculous to state that white bread contains no vitamin B, when yeast, used in the manufacture of white bread, is accepted as being one of the richest sources of this vitamin."

Rats may live a year on white bread, butter, and salts.

The action of vitamin B upon the appetite is most remarkable. Karr[4] stated that some relation exists in the dog between the desire to partake of food and the amount of the so-called water-soluble B vitamin ingested. Cowgill[5] gave to a dog for 83 days a diet which was free from vitamin B. On the 74th day pronounced paralysis set in. Eighteen hours after administering tomato juice decided recovery was effected and the paralysis was completely abolished in 4 days. Several days before the paralysis sets in the dog begins to lose its appetite. Commercial beef extract promotes the flow of gastric juice but does not restore the sense of appetite if vitamin B deficiency exists.[6] The dog's daily requirement of vitamin B is contained in 40 mg. of Harris yeast vitamin concentrate, for a dog

[1] Magendie, F.: Compt. rend. acad. sc., 1841, **13,** 237.
[2] Bell, M., and Mendel, L. B.: Am. J. Physiol., 1922, **62,** 145.
[3] Hartwell, G. A.: Biochem. J., 1924, **18,** 120, 1323.
[4] Karr, W. G.: J. Biol. Chem., 1920, **44,** 255.
[5] Cowgill, G. R.: Am. J. Physiol., 1921, **57,** 420.
[6] Cowgill, G. R., Deuel, H. J., Jr., and Smith, A. H.: *Ibid.*, 1925, **73,** 106.

fed with a diet containing this amount as its sole source of vitamin B has continued in good health for 15 months (Cowgill, Deuel and Smith). The dog received no vitamin C in its diet. The lack of appetite in vitamin B deficiency is also associated with a loss of gastric tone.[1]

How the manner of instinct triumphs is graphically set forth by Tscherkes,[2] who states that polyneuritic fowls refuse to accept kernels of maize sprinkled in a garden but seek at once the vitamin-containing green plants.

One of my colleagues (Murlin), who had set for himself the task of living exclusively upon the same variety of cereal grain, shortly found at breakfast an unsurmountable distaste for the cereal in question, which was cured by a small amount of yeast powder given from the tip of a pen knife. The saliva began to flow and the cereal could be taken with relish.

The effect upon the total metabolism in vitamin B deficiency has been studied by various authors. Abderhalden[3] concluded that the heat production was diminished as the result of avitamosis. Groebbels[4] experimented with mice and concluded that the fall in total metabolism was due to fasting. Anderson[5] worked with hens and was troubled by their restlessness. He obtained the usual respiratory quotients of over unity after giving rice, until a short time before polyneuritis set in. He attributed the fall in heat production to the inability of the animals to utilize the normal quantity of food.

Deuel and Weiss,[6] in experiments not yet published in full, showed that when a dog received a diet free from vitamin B the basal metabolism declined in accordance with the decline in the nutritive state. When the onset of polyneuritic symptoms occurred the metabolism increased on account of the rigidity of the muscles. If vitamin B were given at this point, recovery took place and the dog, cured of polyneuritis and resting quietly in the respiration calorimeter, manifested exactly the same metabolism as before polyneuritis set in. The total metabolism is therefore entirely independ-

[1] Cowgill, G. R., Deuel, H. J., Jr., Plummer, N., and Messer, F. C.: Am. J. Physiol., 1926, **77,** 389.

[2] Tscherkes, L.: Biochem. Z., 1923, **143,** 1.

[3] Abderhalden, E.: Pflüger's Arch. gesam. Physiol., 1920, **182,** 133; 1921, **187,** 80; 1921, **188,** 60.

[4] Groebbels, F.: Z. physiol. Chem., 1922, **122,** 104; 1923, **131,** 214; 1924, **137,** 14.

[5] Anderson, R. J., and Kulp, W. L.: J. Biol. Chem., 1922, **52,** 69.

[6] Deuel, H. J., Jr., and Weiss, R.: Proc. Soc. Exper. Biol. and Med., 1924, **21,** 456.

ent of the presence or absence of vitamin B in the system. This conclusion agrees with more recent work.[1]

Okada and Sakurai,[2] working in Japan, report that in human beriberi normal values for basal metabolism and for the respiratory quotients were obtained. Only when cardiac incompetence threatened did the metabolism increase. In a case in which paralysis and atrophy were outstanding and progressive the basal metabolism fell from a level of +14 to −27 per cent. of the normal in two months; in another case from −7.1 to −30.2 in three weeks. Both of these individuals were cured by administering the vitamin B of rice polishings.

The Chemistry of Vitamin B.—It is stated that vitamin B may pass into the urine, for urine added to the diet will cure polyneuritis in fowls. Animal charcoal absorbs the antineuritic vitamin[3] from urine.

Sherman and Burton[4] state that if vitamin B of tomato juice be heated for 4 hours at 100° C. at its natural acidity of pH 4.28 only 20 per cent. of the original vitamin is destroyed. At a pH of 7.9 between 60 and 70 per cent. of the vitamin is destroyed, while heating one hour only at a pH of 10.9 may completely destroy the vitamin.

Eddy[5] states that he has isolated a crystalline substance melting at 223° C. which he defines as having the properties of a bios.

Levene[6] has obtained a concentrate of vitamin B which contains 15 per cent. of nitrogen and in doses of 0.1 mg. is potent for the growth of rats.

Jansen and Donath,[7] working in Java, have given rice birds (bondals) washed polished rice and developed polyneuritis in them in 9 to 12 days. The administration of 0.002 mg. daily of a material derived from rice bran prevented the polyneuritis. Only 1 mg. daily would be required by man. The authors state that 300 kg. of rice bran yield 100 mg. of the crystalline anti-beriberi-vitamin hydrochlorid used by them.

[1] Roche, J.: Arch. int. physiol., 1925, **24,** 413; Drummond, J. C. and Marrian, G. F.: Biochem. J., 1926, **20,** 1229; Lawrow, B. A. and Matzko, S. N.: Biochem. Z., 1926, **179,** 332.

[2] Okada, S., and Sakurai, E.: Arch. Int. Med., 1926, **38,** 770.

[3] van der Walle, N.: Biochem. J., 1922, **16,** 713.

[4] Sherman, H. C., and Burton, G. W.: J. Biol. Chem., 1926, **70,** 639.

[5] Eddy, W. H., Kerr, R. W., and Williams, R. R.: J. Am. Chem. Soc., 1924, **46,** 2846.

[6] Levene, P. A., and van der Hoeven, B. J. C.: J. Biol. Chem., 1925, **65,** 483.

[7] Jansen, B. C. P., and Donath, W. F.: Med. v. d. Dienst. d. Volksgezondheid in Ned-India, 1927, Part 1, 1.

Truly vitamin B is one of the little things of life which matter greatly.

VITAMIN B AND PELLAGRA PREVENTION

Another deficiency disease is pellagra. Funk[1] states that in the United States between 1907 and 1912, 20,000 persons died of pellagra, the mortality being 40 per cent. among those suffering from the disease. Pellagra occurs in the "corn belt" of the United States, and especially among the poorer classes of the South. The disease has developed since the introduction in 1880 of highly perfected machinery which furnishes corn and wheat completely freed of their outer coverings. In Italy, where the process of milling corn is primitive, the mortality among the pellagrins is only 4 per cent. Nightingale[2] reports that in a prison in Rhodesia, where hand-milled maize was given, this food proved to be adequate, but when maize without its skin was substituted 1210 cases of pellagra occurred. There is no pellagra in zones where the potato is cultivated. Nightingale concluded that the disease was in no way infectious or contagious. Green vegetables, meat, butter, and potatoes are found to be the best antidotes.

Goldberger[3] reports that at an isolated convict camp in Mississippi 11 volunteers were placed on a one-sided diet of highly milled wheat, corn, rice, corn starch, cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips and turnip greens as the result of which 6 individuals developed pellagra after the diet had been administered for about five months. Other prisoners on the usual prison diet were free from it. Hence pellagra is not an infectious disease. Is it due to a faulty mineral supply? to amino-acid deficiency? to lack of vitamin?

Vedder[4] believes that pellagra, like beriberi and scurvy, is a deficiency disease, the deficiency being attributed to a too exclusive use of wheat flour, cornmeal, and other cereals with a minimum consumption of animal proteins. He writes: "If pellagra is a deficiency disease it has an extremely long depletion period. If Goldberger and his associates produced pellagra in their human feeding experiments,

[1] Funk, C.: Münchener med. Wchnschr., 1914, **61**, 698.
[2] Nightingale, P. A.: British Med. J., 1914, Pt. 1, p. 300.
[3] Goldberger, J.: J. Am. Med. Assn., 1916, **66**, 471. Goldberger, J., and Wheeler, G. A.: Arch. Int. Med., 1920, **25**, 451.
[4] Vedder, E. B.: Arch. Int. Med., 1916, **18**, 137; J. Am. Med. Assn., 1916, **67**, 1494.

the depletion periods on the diets used may be placed at at least five months."

The United States Public Health Service maintained for some time an important station at Spartanburg, S. C., in the heart of the pellagra district, and issued several reports which cannot here be detailed.[1]

Goldberger,[2] in a summary of the knowledge on pellagra, relates that the German army of occupation in Roumania during the war, with a personnel of several hundred thousand men, did not contract pellagra, then prevalent there, despite close contact with the Roumanian population and despite the fact that true infectious diseases were readily contracted. In the south of the United States a change in the economic conditions in factory towns induces outbreaks of pellagra. A diet containing a generous allowance of milk and fresh meat is quite regularly followed by improvement. No medication is necessary. Goldberger formerly thought that the protein element was curative, but discovered that when casein was administered it was not effective. However, he has shown that casein and yeast are effective if given to pellagrins. The effective substance in yeast is not the antineuritic vitamin B but is a specific entity which he names the P-P or pellagra-preventative vitamin.

Chick and Roscoe[3] confirm the conception that the water soluble vitamin B is composed of two components: (1) the antineuritic or anti-beriberi vitamin and (2) the vitamin B *stricto sensu* identical with the pellagra-preventive factor of Goldberger. The known materials yielding vitamin B contain both of the above mentioned varieties. However, wheat embryo contains much of the antineuritic and little of the pellagra-preventive vitamin, so if this be given to rats as the sole source of vitamin B, pellagra may be induced in them. This is more readily accomplished if wheat embryo be extracted with alcohol which dissolves the antineuritic more readily than the pellagra-preventive vitamin. When the alcohol extract is added to the diet as a source of vitamin B no paralysis results at the end of the usual time for the onset of the symptoms, but after a much longer period the characteristic dermatitis of pellagra appears on the rats.

[1] Hunter, A., Givens, M. H., and Lewis, R. C.: "Preliminary Observations of Metabolism in Pellagra," Hygienic Laboratory, Bulletin 102, 1916; Koch, M. L., and Voegtlin, C. "Chemical Changes in the Central Nervous System as a Result of Restricted Vegetable Diet," Hygienic Laboratory, Bulletin 103, 1916.

[2] Goldberger, J : Med., 1926, **5**, 79.

[3] Chick, H., and Roscoe, M. H.: Biochem. J., 1927, **21**, 698.

This is a highly satisfactory solution of an important problem of public health which has occupied the attention of many students of high ability for many years. It has so wholly occupied the attention of Goldberger for over a decade that it is gratifying that it is he who has pointed to the way out of the wilderness and that the admirable group of workers at the Lister Institute, London, have participated in the advance.[1]

VITAMIN C

In 1912 Holst and Frölich[2] reported that if guinea-pigs were fed with a one-sided diet of white bread, or with polished rice or other milled grains, they invariably died, usually in about four weeks. They always showed loose teeth and usually hyperemic gums. Hemorrhages appeared, sometimes in the skin, but more usually at the knee-joints and at the cartilages of the ribs, and there were microscopic changes in the bone-marrow. All these phenomena are in entire accord with the manifestations of human scurvy. It is important to remember that it has never been demonstrated that any kind of unmilled grain allows the onset of scurvy. The pericarp, therefore, contains materials essential to health. As antidotes to foods which produce scurvy, fresh vegetables, dried peas, lime juice, or fermented liquors (wines, beer) are antiscorbutic and cure human scurvy as well as the form artificially induced in animals. Drying or heating some of the effective substances to 110° reduces the antiscorbutic effect.

Hess[3] reports that in an asylum where infants were fed with pasteurized milk during a period of four months scurvy developed, accompanied by a stunting in the normal growth of the infants. This was at once corrected by the administration of orange juice.

Lemon juice was early found to be a preventive of scurvy, and its introduction into the British Navy in 1795 led to the disappearance of the disease among the sailors.

Holst[4] describes how Cartier on his second voyage to Newfoundland, in 1535, administered with great success a fresh decoction of

[1] Concerning pellagra in dogs consult Underhill, F. P. and Mendel, L. B.: Am. J. Physiol., 1928, **83**, 589.

[2] Holst, A., and Frölich, T.: Z. f. Hyg., 1912, **72**, 1.

[3] Hess, A. F.: Proc. Soc. Exper. Biol. and Med., 1915–16, **13**, 50; also Hess, A. F.: "Scurvy Past and Present," Philadelphia and London, 1920.

[4] Holst, A.: XVth International Congress of Hygiene, Washington, 1913, **2**, 588.

pine needles to a crew of 103 men of whom only 3 were free from scurvy. Holst states that when the Eskimos suffer from this disease they turn to the liver of seals or, better, to fresh "matok," which is the rete Malpighii of the skin of whales.

During the siege of Paris scurvy broke out on a large scale on account of the prolonged one-sided diet of farinaceous nutriment. Under ordinary conditions in civilized communities scurvy is of rare occurrence, although it has been known to develop in poorhouses which have been placed under ignorant or dishonest control.

Since the pioneer work of Holst the guinea-pig has been the principal animal used in the study of scurvy. If young guinea-pigs are placed on a diet which is lacking in vitamin C they may gain in weight for a couple of weeks and then lose weight rapidly and die of scurvy within a month. Chick and Hume[1] showed that when guinea-pigs received a diet of rolled oats and hay they did not develop scurvy if raw milk was added to the diet. This was confirmed by Hart, Steenbock, and Smith.[2]

Confusion of interpretation was early introduced by the fact that rats did not contract scurvy,[3] but it was soon shown by Parsons[4] that rats already contained vitamin C in their livers. Other investigators[5] have confirmed this, showing that young rats, when taking a ration free from antiscorbutic vitamin for 114 days, still have sufficient antiscorbutic vitamin in their livers so that 1 gm. of rat liver substance fed to guinea-pigs will cure them of scurvy. Not only this, but the second generation of offspring of rats nourished throughout upon a diet free from vitamin C still have livers rich in this vitamin. It appears, therefore, that the rat can manufacture vitamin C in its liver. The same is true of mice[6] and of dogs (see p. 497).

Plimmer and Rosedale[7] have kept pigeons 15 months on diets free from vitamin C, during which time the animals laid eggs and reared young. They reared chickens from their first day of life on a similar diet, and the animals laid eggs, some of which hatched. Ducks, geese, guinea-fowl, and pheasants, all indicate that the ingestion of vitamin C is unnecessary for normal life.

[1] Chick, H., and Hume, M.: Trans. Soc. Trop. Med. and Hyg., 1916–17, **10,** 141.
[2] Hart, E. B., Steenbock, H., and Smith, D. W.: J. Biol. Chem., 1919, **38,** 305.
[3] McCollum, E. V., and Pitz, W.: *Ibid.*, 1917, **31,** 229.
[4] Parsons, H. T., and Hutton, M. K.: *Ibid.*, 1924, **59,** 97.
[5] Lepkovsky, S., and Nelson, M. T.: *Ibid.*, 1924, **59,** 91.
[6] Beard, H. H.: Am. J. Physiol., 1925–26, **75,** 668.
[7] Plimmer, R. H. A., and Rosedale, J. L., with Raymond, W. H.: Biochem. J., 1923, **17,** 787.

Chickens thus reared possess in their livers antiscorbutic substances of their own manufacture.[1]

Hess and Unger[2] found that the juice of canned tomatoes was as good an antiscorbutic as orange juice and commended it for children on account of its cheapness.

Barnes and Hume[3] state that summer cows' milk, produced from a diet of fresh herbage, has a higher antiscorbutic value than winter cows' milk, produced from a diet of hay, oil cake, cereals, and roots. When the latter is taken in the diet the addition of orange juice, tomatoes, or tinned tomatoes is recommended. Hart, Steenbock, and Ellis[4] confirm the observation that summer pasture milk is much richer in vitamin C than dry feed milk or winter milk produced from a diet containing corn silage or sugar mangolds. However it has lately been stated that there is no relation between the vitamin C content of a cow's ration and the content of this vitamin in its milk, and that the cow manufactures vitamin C.[5]

Hart, Steenbock, and Ellis also state that all milk powders should be supplemented with potent sources of antiscorbutic vitamin. This is different from the conclusion reached by Barnes and Hume as to the antiscorbutic potency of dried milk. Supples and Dow[6] find that, whereas reconstituted spray process whole milk powder has lost much of its antiscorbutic power, dry milk by the Just roller process, when stored in the air at room temperature for two years, has an antiscorbutic value equal to that of fresh milk. Humphrey[7] finds that dried orange juice still preserves its vitamin C content after five years' storage.

Cabbage contains vitamin C, but sauerkraut has lost it.[8] Raw potatoes, baked potatoes, and even dried potatoes contain the vitamin.[9] Beef contains little or none.[10] However Stefansson, the Arctic explorer, states (oral communication) that an exclusive diet of meat

[1] Carrick, C. W., and Hange, S. M.: J. Biol. Chem., 1925, **63,** 115.
[2] Hess, A. F., and Unger, L. J.: *Ibid.*, 1919, **38,** 293.
[3] Barnes, R. E., and Hume, E. M.: Biochem. J., 1919, **13,** 306.
[4] Hart, E. B., Steenbock, H., and Ellis, N. R.: J. Biol. Chem., 1920, **42,** 383; 1921, **46,** 309.
[5] Hughes, J. S., Fitch, J. B., Cave, H. W., and Riddell, W. H.: *Ibid.*, 1926–27, **71,** 309.
[6] Supples, G. L., and Dow, O. D.: Am. J. Dis. Child., 1926, **31,** 41.
[7] Humphrey, G. J.: J. Biol. Chem., 1926, **69,** 511.
[8] Ellis, N. R., Steenbock, H., and Hart, E. B.: *Ibid.*, 1921, **46,** 367.
[9] Givens, M. H., and McClugage, H. B.: *Ibid.*, 1920, **42,** 491.
[10] Dutcher, R. A., Pierson, E. M., and Biester, A.: *Ibid.*, 1920, **42,** 301.

and fat, though persisted in for many months, will not produce scurvy in man.

Zilva[1] has prepared from lemon juice a solution containing 0.03 to 0.07 per cent. of solids which has the same antiscorbutic potency as the original lemon juice.

Sherman[2] believes that much of the so-called rheumatism which affects many of our people living in the country during the winter is due to a lack of vitamin C in their dietaries.

The milk fed baby instinctively craves orange juice, and we have been told of the delight with which Clemenceau partook of American grape fruit while he was in this country.

VITAMIN D AND RICKETS

A decade ago little was known regarding the etiology of rickets. Since that time "despite of war and wasting fire" our knowledge has vastly increased. Great pictures of this disease have been drawn by Howland[3] and by Park.[4] Rickets has long been known as a disease of the bones which is painfully prevalent among city bred children.

Hess and Unger[5] reported a striking example of the influence of the migration of poor West Indian families to New York City upon the incidence of rickets among them. In their former homes, living largely in the sunlight and partaking of fresh fruits and vegetables, rickets was unknown among them, whereas living in darkened rooms and alleys in New York and partaking of bread, meat, and potato, with very little milk, their offspring, though nursed by their mothers, were all rachitic.

From time immemorial the inhabitants of Norway during the long dark winters have given their children cod-liver oil on purely empirical grounds.

The long and extensive researches of Findlay[6] led him to believe that lack of muscular exercise was a dominant cause of rickets.

In 1912 Raczynsky[7] reported upon *lack of sunlight* as a cause of rickets, for he had taken two puppies, born in May of the same litter

[1] Zilva, S. S.: Biochem. J., 1924, **18**, 632.
[2] Sherman, H. C.: "Chemistry of Food and Nutrition," 3d ed., New York, 1926, p. 438.
[3] Howland, J.: Med., 1923, **2**, 349.
[4] Park, E. A.: Physiol. Rev., 1923, **3**, 106.
[5] Hess, A. F., and Unger, L. J.: J. Am. Med. Assn., 1918, **70**, 900.
[6] Findlay, L.: *Ibid.*, 1924, **83**, 1473.
[7] Raczynsky, J.: Compt. rend. assoc. intern. pédiatrie, 1912, 308.

and suckled by the same mother, and reared one in the dark and one in the light and found that the one reared in darkness developed rickets and the other did not.

Mellanby[1] in 1918 reported that rickets was due to a diet which lacked an accessory factor. In a more extended communication he[2] reports that puppies fed with bread, separated milk, linseed oil, yeast, and orange juice developed rickets, whereas if cod-liver oil or butter fat were administered rickets was prevented. Mellanby concluded that vitamin A and the antirachitic vitamin were identical. This was pioneering work, opening the field for others to tread.

Another factor of interest is that in 1917 the late John Howland[3] published a paper on the diminished calcium content of the blood in infantile tetany, and he told me at that time that he proposed to carry such methods into the field of rickets, that he chose the line of work because no one was then interested in rickets. He also was another great pioneer.

In 1922 McCollum, Simmonds, Becker, and Shipley[4] showed experimentally that cod-liver oil, oxidized for 12 or 20 hours, did not cure xerophthalmia in rats, whereas it did cause the deposition of calcium in the bones of young rats suffering from rickets. They therefore disputed Mellanby's contention that vitamin A and the antirachitic vitamin were identical.

In the same year McCollum, Simmonds, Shipley, and Park[5] described a delicate biological test for calcium depositing substances. Their rickets producing diet was free from vitamin D, was low in its content of P_2O_5 and relatively high in Ca, a diet which Sherman and Pappenheimer[6] had shown to be very potent in producing rickets. Such a diet uniformly caused the bones of animals fed on it to be free from calcium as regards the epiphyseal cartilages and the metaphyses and created the picture of florid rickets. When to this diet 2 per cent. of cod-liver oil was added rickets was cured. Hence, cod oil was a calcium depositing substance. In the words of McCollum and his colleagues,

[1] Mellanby, E.: Proc. Physiol. Soc., J. Physiol., 1918–19, **52**, p. xi.
[2] Mellanby, E.: Med. Research Council Special Report Series, 1921, No. 61.
[3] Howland, J., and Marriott, W. McK.: Quart. J. Med., 1917–18, **11**, 289.
[4] McCollum, E. V., Simmonds, N., Becker, J. E., and Shipley, P. G.: J. Biol. Chem., 1922, **53**, 293.
[5] McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A.: *Ibid.*, 1922, **51**, 41.
[6] Sherman, H. C., and Pappenheimer, A. M.: Proc. Soc. Exper. Biol. and Med., 1920–21, **18**, 193.

"This test depends on the power of a given substance to cause the reappearance of a provisional zone of calcification in epiphyseal cartilages of animals with very severe rickets, whose cartilages had been rendered calcium-free by faulty diets. We called this procedure the "line test," because in gross specimens or in histological preparations the new zone of calcification appears as a line of calcified tissue crossing an area which is free from lime salt deposits."

The rickets producing diet 3143 was made up of soft wheat, 33 per cent.; maize, 33 per cent.; gelatin, 15, wheat gluten, 15, sodium chlorid, 1, and calcium carbonate, 3 per cent.

Park and Howland[1] were the first to show by means of X-ray observations that when cod-liver oil was administered to children with rickets curative results were discernible in 2 or 3 weeks.

It has been shown by Hart, Steenbock, and Hoppert[2] that pasturage greatly increases the capacity for calcium deposition in cattle. And later from the same laboratory[3] it was shown that a dairy cow, bred to a high milk producing capacity (20 to 27 liters daily), cannot maintain its calcium requirement under a natural environment of feed and sunlight but must receive extra antirachitic vitamin to prevent lowering of the milk flow, impairment of health, poor calf production, nutrition abortion, or sterility.

Korenchevsky and Carr[4] state that the presence of cod oil and calcium and phosphorus in the diet of rats is of great benefit to the young, during both the pregnancy and lactation of the mother.

Chick and Roscoe[5] have investigated the influence of diet and sunlight upon the vitamin content in the milk afforded by a cow and report as follows:

Vitamin A.	Maximum: Diet of fresh green food.
	Minimum: Diet of cereals and roots.
	Sunlight no influence.
Vitamin D.	Maximum: Pasture fed.
	Minimum: Diet of roots and cereals.
	Sunlight little influence.

When the cows were given green fodder in a dark stall there was the same amount of vitamin A in the milk as when the cow was

[1] Park, E. A., and Howland, J.: Johns Hopkins Hosp. Bull., 1921, **32**, 341.
[2] Hart, E. B., Steenbock, H., and Hoppert, C. A.: J. Biol. Chem., 1921, **48**, 33.
[3] Hart, E. B., Steenbock, H., Elvehjem, C. A., Scott, H., and Humphrey, G. C.: *Ibid.*, 1926, **67**, 371.
[4] Korenchevsky, V., and Carr, M.: Biochem. J., 1925, **19**, 112.
[5] Chick, H., and Roscoe, M. H.: *Ibid.*, 1926, **20**, 632.

exposed to sunshine. "But when the cow is out at pasture the fresh green food together with the exposure to sunlight apparently combine to raise the vitamin D content of the milk to a higher level than can be effected by direct sunshine alone." The moral is drawn that milch cows ought not to be kept in stalls when their milk is used by infants and children.

In similar vein another set of workers[1] have defined the influence of pasture on pigs.

"Pasture proved the one best practical corrective of a grain ration. Pasture furnished abundant vitamins, easily assimilable minerals, and favorable proteins. It automatically provided soil in which to root, and, last but not least, allowed exposure to direct sunlight. Pigs bathed in sunlight in the open made better gains and grew denser and stronger bones than pigs fed the same rations but kept indoors."

It was Mrs. May Mellanby[2] who first called attention to the influence of the diet upon the production of caries. E. Mellanby[3] has recently written "that food containing fat soluble vitamins, such as milk, egg-yolk, butter, animal and fish fats, and especially cod-liver oil, bring about the formation of good teeth, while cereals, and especially oatmeal, in the absence of calcifying vitamin, bring about the formation of defectively calcified teeth." The maternal condition should be fortified by proper foods to produce proper calcification in the young. These principles are strongly supported by Mrs. Mellanby's evidence regarding the influence of the diets of children upon the soundness of their teeth.

Hess and Matzner[4] suggest as a proper modification of cow's milk the addition of 21 c.c. of lemon juice to the liter, thereby changing its pH from 6.64 to 5.54. This makes it more digestible, more like human milk, and furnishes vitamin C. Egg yolk in addition gives more of vitamins A and D and iron as well.

The Effect of Light.—Huldschinsky[5] was the first to demonstrate that the ultra-violet rays of the sun would cure rickets. Prior to that time cod-liver oil was the only recognized remedy. Hess and

[1] Bohstedt, G., Bethke, B., Edgington, B. H., and Robison, W. L.: Bull. Ohio Agricul. Exp. Sta., 1927, **12**, 67.

[2] Mellanby, M.: Dental Record, 1920, **40**, 65.

[3] Mellanby, E.: British Med. J., 1926, p. 515. Consult also M. Mellanby and Pattison, C. L.: British Dental J., October, 1926.

[4] Hess, A. F., and Matzner, M. J.: J. Am. Med. Assn., 1924, **82**, 1604.

[5] Huldschinsky, K.: Deut. med. Wochenschr., 1919, **45**, 712.

Unger,[1] using the X-ray, demonstrated that ultra-violet light and the sun's rays cured children of rickets. Chick and Dalyell,[2] working in Vienna after the war, clearly showed that rachitic children receiving a usual milk diet could not be cured if left in the hospital wards. When cod-liver oil was given to them or they were placed on the roof in the sunshine, the rickets was healed. Ordinary glass windows do not admit the ultra-violet rays of the sun.

Orr, Holt, Wilkins, and Boone[3] have compared the absorption of calcium and phosphorus by a rachitic child before and after ultra-violet irradiation. Before treatment during a period of 4 days there were negative calcium and phosphorus balances of 0.1 and 0.01 gm., respectively. On the other hand, after irradiation 2.81 gm. of calcium and 1.79 gm. of phosphorus, or about 50 per cent. of the amounts in the ingesta, were retained by the child.

This is interesting in the light of the fact that Telfer[4] has shown that there is no difference in the Ca and P_2O_5 content of the milk of Glasgow women whose children do or do not have rickets; and also that the milk of country women in neighboring villages is not different in these constituents from the milk of the city women.

Hess and Weinstock[5] found that the curative antirachitic rays lay in the neighborhood of wave lengths between 300 and 313 microns. Hess and Weinstock[6] furthermore showed that when linseed and cotton seed oil, which are devoid of vitamin D, are irradiated by ultra-violet light, they become potent antirachitic agents. Irradiated lettuce leaves were also antirachitic. Wheat grown in the dark had no antirachitic properties, but grown under a mercury vapor lamp acquired them. The same authors[7] discovered that irradiated cholesterol prevents rickets, and attributed the effect of light upon the skin to absorption of ultra-violet rays by cholesterol. Kramer[8] found that after the irradiation of cow's milk for 10 to 20 minutes it acquired properties which would cure rickets in children.

[1] Hess, A. F., and Unger, L. J.: Proc. Soc. Exper. Biol. and Med., 1920–21, **18,** 298.
[2] Chick, H., Dalyell, E. J., Hume, E. M., Mackay, H. M. M., Smith, H. H., and Wimberger, H.: Med. Research Council Bull. Special Report Series No. 77, 1923, p. 19; Chick, H., Dalyell, E. J., Hume, E. M., and Mackay, H. M. M., Lancet, 1922, 2, 7.
[3] Orr, W. J., Holt, L. E., Jr., Wilkins, L., and Boone, F. H.: Am. J. Dis. Child., 1923, **26,** 362.
[4] Telfer, S. V.: Biochem. J., 1924, **18,** 809.
[5] Hess, A. F., and Weinstock, M.: J. Am. Med. Assn., 1923, **80,** 687.
[6] Hess, A. F., and Weinstock, M.: J. Biol. Chem., 1924–25, **63,** 301.
[7] Hess, A. F., and Weinstock, M.: *Ibid.*, 1925, **64,** 181.
[8] Kramer, B.: Am. J. Dis. Child., 1925, **30,** 195.

Rosenheim and Webster[1] have irradiated cholesterol and have found that 5 mg. were required daily to prevent the appearance of rickets. Moreover, they separated from the activated cholesterol an amorphous substance which prevented rickets in rats in doses of 0.001 mg. daily. And Hess and Windaus[2] have found that if cholesterol be purified it may fail to develop antirachitic properties after irradiation, but that another constituent, ergosterol, an optically active sterol with three double bonds and a hydroxyl radicle, when irradiated and fed to rats, brings about a healing process in the bones when given in amounts of 0.003 mg. daily. Windaus refers to ergosterol as a pro-vitamin, a substance which probably undergoes a chemical transformation through the action of ultra-violet rays and is converted into the antirachitic vitamin D.

Ultra-violet irradiation of a nursing woman brings about marked increase in the antirachitic potency of her milk.[3]

The high value of sunshine is apparent, but industrialized mankind gets little of it. Houses are glass windowed cages through which the ultra-violet rays do not pass. But special glass has been made 3 to 5 mm. thick which allows as much as 80 per cent. of the light radiations curative of rickets to pass.[4] Other commercial glass, made of quartz, allows at most one-half of these rays to pass. It is stated that the only glass of this kind which does not deteriorate is that of quartz, and quartz glass is very costly. "Celanese" and other artificial silks allow the ultra-violet rays to pass.

The Blood Salts in Rickets.—In 1920 Kramer and Howland[5] published a method for the determination of calcium in small quantities of blood serum and they confirmed Howland and Marriott's observation that in infantile tetany the calcium in the serum is subnormal. Using this method, Kramer, Tisdall, and Howland[6] found that, whereas the calcium content of normal blood serum is 10 to 11 mg. per 100 c.c., in tetany complicated with rickets the amount falls to 5.4 mg. or half the normal quantity. But in rickets uncomplicated by tetany Howland and Kramer[7] showed that the calcium content of the blood serum was normal but that the phosphate concentration

[1] Rosenheim, O., and Webster, T. A.: Biochem. J., 1926, **20**, 537.
[2] Hess, A. F., and Windaus, A.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 461.
[3] Hess, A. F., Weinstock, M., and Sherman, E.: J. Am. Med. Assn., 1927, **88**, 24.
[4] Luce, E. M.: J. Biol. Chem., 1926–27, **71**, 187.
[5] Kramer, B., and Howland, J.: *Ibid.*, 1920, **43**, 35.
[6] Kramer, B., Tisdall, F. F., and Howland, J.: Am. J. Dis. Child., 1921, **22**, 431.
[7] Howland, J., and Kramer, B.: *Ibid.*, 1921, **22**, 105.

was always below the normal of 5 mg. phosphorus per 100 c.c. This was shown independently by Iversen and Lenstrup.[1] In extreme cases of rickets the inorganic phosphorus of the blood may sink as low as 1 mg. per 100 c.c.

The work of Howland and Kramer and of Iversen and Lenstrup showed that the administration of cod-liver oil to children in this condition increased the inorganic phosphorus of the serum, and Howland and Kramer[2] showed that irradiation accomplished the same result.

In rats the same principles hold true except that uncomplicated rickets is induced either by low calcium or by low phosphorus,[3] for rats do not suffer from tetany.

The surgeon should realize the importance of this knowledge in the healing of fractures, and this aspect of the situation has been experimentally demonstrated by Petersen.[4]

A wonderful experiment was announced from Howland's children's clinic by Shipley[5] in 1924. He demonstrated that, if an isolated piece of bone of a rachitic rat be placed in serum or plasma taken from normal rats, calcification begins in the bone in 48 hours. The new deposits of calcium are apparently similar to those which are found in bones taken from the bodies of rats with healing rickets. And later Shipley, Kramer, and Howland[6] demonstrated that calcification of rachitic cartilage took place within 9 hours when it was put in an aqueous solution containing, in 100 c.c., calcium, 10 mg., inorganic phosphorus, 4 mg., at a pH between 7.05 and 7.4. Boiling destroyed the capacity of the tissue to form bone. Calcification therefore occurred *in vitro* exactly the same as it does *in vivo*. Rachitic bones placed in aqueous solutions containing calcium salts and inorganic phosphates calcify rather rapidly only when the concentration of the bone-forming constituents and the reaction of the buffered solution are nearly the same as in normal serum. Calcification takes place when normal serum is used. The process is clearly not one of simple precipitation for it depends on the activity of living tissue. It cannot occur unless the concentration of calcium and

[1] Iversen, P., and Lenstrup, E.: Forhandlingerne ved Første Nordeske Kongress for Pediatrie, 1920.

[2] Howland, J., and Kramer, B.: Johns Hopkins Hosp. Bull., 1922, **33**, 313.

[3] McCollum, E. V., *et al:* J. Biol. Chem., 1920–21, **45**, 333; 1921, **47**, 507.

[4] Petersen, H. A.: Johns Hopkins Hosp. Bull., 1924, **35**, 378.

[5] Shipley, P. G.: *Ibid.*, p. 304.

[6] Shipley, P. G., Kramer, B., and Howland, J.: Am. J. Dis. Child., 1925, **30**, 37; Biochem. J., 1926, **20**, 379.

phosphorus in the serum exceeds a certain minimal value. The primary failure of calcification in rickets does not depend on any primary inability of rachitic bone to undergo calcification. The failure depends on an insufficient concentration of the necessary elements in the fluids bathing these tissues.

These words represent the climax of achievement of the great and beneficent career of John Howland, the head of a children's clinic unequalled in its day, who died in middle life at a time when he could ill be spared.

Fries[1] states that therapeutic doses of ultra-violet radiation have no effect on the basal metabolism of children (see p. 142).

THE FERTILITY VITAMIN E

Evans and Bishop[2] discovered that rats which grew perfectly well upon a diet of casein, lard, starch, salts, yeast, and vitamin A were usually sterile, and the next generation was always sterile. The sterility could be cured by adding small doses of wheat germ oil to the diet. Other substances—meat, lettuce and other green leaves, whole wheat, and milk fat—relieve the condition. This work has been confirmed by Sure.[3] Mattill and Clayton[4] state that wheat germ oil will always cure the sterility in female rats, but if the testes have degenerated the sterility cannot thus be cured in the male.

Simmonds, Becker, and McCollum[5] say that the death of the fetuses in rats on diets deficient in vitamin E is due to a crisis in their iron assimilation, which is avoided by giving enough vitamin E during pregnancy.

THE BIOLOGICAL VALUE OF VARIOUS PROTEINS

Since purified protein may be given free from phosphorus without prejudice to the capacity to grow, it is evident that an animal, when fed with a diet of pure protein, carbohydrate, fat, and simple inorganic salts, may produce synthetically lecithin, phosphatids, nuclear material (purins, etc.), hemoglobin, and bone-tissue.

[1] Fries, M.: Am. J. Dis. Child., 1927, **34**, 159, 166.
[2] Evans, H. M., and Bishop, K. S.: J. Metab. Res., 1922, **1**, 319, 335; 1923, **3**, 201, 233.
[3] Sure, B.: J. Biol. Chem., 1923–24, **58**, 693.
[4] Mattill, H. A., and Clayton, M. M.: *Ibid.*, 1926, **68**, 665.
[5] Simmonds, N., Becker, J. E., and McCollum, E. V.: J. Am. Med. Assn., 1927, **88**, 1047.

McCollum states that he has never seen growth enhanced by the addition of organic phosphorus to a diet. Certain amino-acids, however, must be furnished preformed. Mendel and Osborne and McCollum and Davis are in essential accord with regard to these underlying principles, and science owes them much for their laborious and painstaking contributions to this long obscure chapter of dietetics.

In another chapter of this book (see p. 190) the unequal nutritional value of the proteins, such as are found in meat or gelatin, has been emphasized. This difference in nutritive value was set forth by Karl Thomas,[1] who took starch and sugar in large quantity in his diet, determined the minimal loss of body protein under these circumstances, and then added to the diet food materials containing different proteins, in order to determine their relative power in sparing the body from a loss of tissue protein. The values given below Thomas named the *biologic values* of the proteins employed:

BIOLOGIC VALUES OF DIFFERENT PROTEINS, AS MEASURED BY THE PERCENTAGE QUANTITY OF BODY PROTEIN WHICH THEIR INGESTION WILL SPARE FROM LOSS

Ox meat	104	Cherry-juice	79
Cows' milk	100	Yeast	71
Fish	95	Casein	70
Rice	88	Nutrose	69
Cauliflower	84	Spinach	64
Crab meat	79	Peas	56
Potatoes	79	Wheat flour	40
		Cornmeal	30

These excellent experiments show clearly the superior value of meat, fish, and milk proteins as conservers of body protein when contrasted with the ordinary group of vegetable proteins.

The dietary value of the various proteins is a matter of considerable interest, and much work has been done, especially regarding the value of potato and of wheat protein. The older work of Hindhede upon the value of potato protein has already been cited.

In 1915 Abderhalden[2] brought a subject into nitrogen equilibrium on a diet of potatoes containing 4.5 gm. potato nitrogen or 0.074 gm. nitrogen per kilogram of body weight. In 1917 Rose and Cooper[3] established nitrogen equilibrium in a young woman weighing 50 kg. when the diet contained 1500 gm. of potatoes (4.97 gm. nitrogen), 50

[1] Thomas, K.: Arch. f. Physiol., 1909, p. 219.

[2] Abderhalden, E., Ewald, G., Fodor, A., and Rose, C.: Pflüger's Arch. gesam. Physiol., 1915, **160**, 511.

[3] Rose, M. S., and Cooper, L. F.: J. Biol. Chem., 1917, **30**, 201.

gm. of butter, and 41 to 61 gm. of cane sugar. The nitrogen intake was 0.096 gm. per kilogram body weight.

Lauter and Jenke[1] have reduced the nitrogen elimination to the minimal level of the wear and tear quota and then compared the relative protective power of meat protein and potato protein upon this factor. The periods were of three or more days. The following comparisons may be made:

Variety of Protein in Diet	Meat	Meat	Potato	Potato	Potato	Wheat
N in gm. in urine and feces.....	3.3	3.85	4.1	3.7	3.93	5.4
N in gm. in the diet.....	2.2	3.4	2.4	2.35	3.3	2.4
Losses of body N, gm.....	−1.1	−0.45	−1.7	−1.35	−0.63	−3.0
Losses of body N in urine + feces on N-free diet, gm.....	−3.1	−3.5	−3.55	.....	−3.8	−3.2

The authors, on the basis of these experiments, agree with Rubner (see p. 58) that Hindhede is wrong in attributing to potato and to wheat protein the same quality as to meat protein. As regards wheat, the same conclusion had been reached earlier in some delightfully described experiments of Martin and Robison.[2] They refer to the man who was the subject of Abderhalden, already mentioned, as a person who chewed each bolus of wheaten bread 120 times before swallowing. "This Hofrat who chewed so long and so well," as they say, found that 9 gm. of nitrogen in wheat bread was not sufficient to maintain nitrogen equilibrium, but that 10.8 gm. nitrogen in rye bread was fully sufficient. Moreover, Neumann[3] maintained himself in nitrogen equilibrium for 7 months when taking 7 gm. of nitrogen in rye bread.

Martin and Robison write that such experiments seem simple but are not so in fact. One of them endeavored to match Neumann's intake of 73 calories per kilogram body weight and thus writes of the event: "It is by no means easy for one of the meagre habit of the subject of the experiment, as it increases the distaste for the sufficiently unappetizing ration of starch and lactose and if persisted in too enthusiastically it produces unpleasant symptoms." The basic diet contained vitamins A in butter fat or cod oil, B in yeast, C in lemon juice, and agar agar was also given. The total calories of the ingesta were 40 to 45 per kilogram body weight. Two experi-

[1] Lauter, S., and Jenke, M.: Deut. Arch. klin. Med., 1925, **146**, 173.
[2] Martin, C. J., and Robison, R.: Biochem. J., 1922, **16**, 407.
[3] Neumann, R. O.: Vierteljahresschrift gerichtlicher Med., 1919, **57**, 1.

ments may be cited as showing the method of analyzing the biological value of milk protein. The averages are those of the last 3 or 4 days of a diet taken continuously for a week or more.

MINIMUM N EXPENDITURE

	Food N	Urine N	Feces N	Total N	N ± Body	Biological Value
	Gm.	Gm.	Gm.	Gm.	Gm.	Per Cent.
Wear and tear quota	0.34	2.34	1.17	3.51	−3.17	
Milk, 3.15 gm. N	3.42	3.12	1.29	4.41	−0.99	73.6
Milk, 6.65 gm. N	6.84	5.61	1.28	6.89	−0.05	48.8

The biological value of a protein is the number of parts of body protein spared by 100 parts of food protein. Thomas' formula reads:

$$\frac{\text{Balance N minimum diet} - \text{balance N protein diet}}{\text{N intake} - (\text{Feces N protein diet} - \text{feces N protein-free diet}) + \text{N intake minimum diet.}}$$

In the first experiment given above these values would be:

$$\frac{(3.17 - 0.99)}{3.42 - (1.29 - 1.17) - 0.34} = \frac{2.18}{2.96} = 73.6 \text{ per cent.}$$

It is evident that by this method "biological values" are greater the nearer the nitrogen of the ingesta approaches the nitrogen of the wear and tear quota. When nitrogen equilibrium is attained the biological value of the protein appears to be less. The average result of 3 experiments near the level of nitrogen equilibrium showed that the value for milk protein is 51.8 per cent. in contrast with 31.9 per cent. for whole wheat bread. The results are thus epitomized:

	Biological Value of Protein	
	Whole Wheat Bread	Milk
	Per Cent.	Per Cent.
C. J. M.	31.9	51.8
R. R.	28.2	23 to 84

Mitchell[1] has reported another method which is based on the ability of a growing animal to retain protein ingested. According to these experiments milk protein may demonstrate a biological value

[1] Mitchell, H. H.: J. Biol. Chem., 1923–24, **58**, 873, 905; Mitchell, H. H., and Beadles, J. R.: *Ibid.*, 1926–27, **71**, 429.

of 85 per cent., potato protein 67 per cent., while beef heart, kidney, and liver are intermediate, 74 to 77 per cent.

There is no doubt that the existing evidence is against Hindhede's[1] contention that bread protein is as good as meat and milk protein.

When the proteins of bread are supplemented with animal proteins excellent results are obtained in growing rats. Thus, McCollum, Simmonds, and Parsons[2] write, "We were surprised to find how consistently combinations of milk proteins and cereal and legume proteins fail to show as high biological values as can be demonstrated for kidney, liver, and muscle proteins combined with those of certain cereals."

Sherman and Campbell[3] show that increasing the quantity of whole milk powder in a whole wheat ration increases the ability to grow a definite number of grams per 1000 calories in the diet ingested. The experiment was as follows:

Diet A. $\frac{1}{6}$ whole milk powder; $\frac{5}{6}$ ground whole wheat.
Diet B. $\frac{1}{3}$ whole milk powder; $\frac{2}{3}$ ground whole wheat.

The growth in grams per 1000 calories consumed in food during the 5th to the 8th weeks, inclusive, of the rats' lives was as follows:

	Increase in Weight	
	Diet A	Diet B
Number of Rats	Gm.	Gm.
50 in each lot	66	79

Hartwell[4] tells us that the proteins of oatmeal are of good value for the growth of rats but are insufficient for gestation and lactation. The protein supply of white bread is inadequate, and with potato alone there is slow growth or none at all. All these diets require supplements of casein, egg albumin, or similar protein to make them sufficient.

THE REASONS FOR THE BIOLOGICAL DIFFERENCES IN PROTEINS

The reason for this biologic difference lies in the amino-acid content of the different proteins, as has been beautifully shown in

[1] Hindhede, M.: Biochem. J., 1926, **20**, 330.
[2] McCollum, E. V., Simmonds, N., and Parsons, H. T.: J. Biol. Chem., 1921, **47**, 235.
[3] Sherman, H. C., and Campbell, H. L.: *Ibid.*, 1924, **60**, 5.
[4] Hartwell, G. A.: Biochem. J., 1925, **19**, 75; *Ibid.*, 1926, **20**, 751, 1273; *Ibid.*, 1927, **21**, 282.

experiments with growing animals. Willcock and Hopkins[1] were the pioneers in this field. They prepared a diet in which *casein* was the sole nitrogenous constituent and obtained good growth in mice when this diet was administered to them. When *zein*, the principal protein of corn, was substituted for casein in the diet, the animals declined and died in about seventeen days. Addition of tyrosin, which zein contains in plentiful amount, was without effect upon the length of life. When, however, tryptophan, which, as well as lysin and glycin, is absent from the zein molecule, was added to the diet in an amount equal to 2 per cent. of the total zein given, the animals lived thirty-two days. Hopkins suggests the possibility that in the absence of tryptophan epinephrin cannot be formed and collapse follows. Osborne and Mendel[2] have maintained a rat at an almost constant body weight of 50 grams for one hundred and eighty-two days on a food containing zein as its dominant protein, with the addition of tryptophan equal to 3 per cent. of the zein. Since zein is free from the amino-acid lysin, it seemed possible that normal growth might be obtained when the protein in the dietary consisted of zein supplemented by tryptophan and lysin; such, indeed, proved to be the case (Fig. 28).

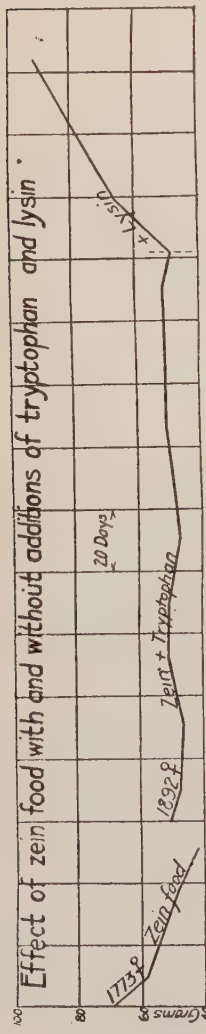


Fig. 28.—Showing *nutritive decline* on zein food, *maintenance* after addition of tryptophan, *growth* after addition of both tryptophan and lysin. Rat 1892 was maintained during one-half year without significant change in body weight on the zein + tryptophan food. Despite this inadequate diet the capacity to grow was not lost at the end of this prolonged period, and the animal ultimately grew to full adult size on a mixed diet.

A striking detail of this work is that at the beginning of the experiment a patch of hair on the animal's back was dyed red and this color remained unchanged for six months. When lysin was added to the diet and growth was resumed the color soon disappeared.

[1] Willcock, E. G., and Hopkins, F. G.: J. Physiol., 1906–07, **35**, 88.
[2] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1915, **20**, 351.

New growth became possible in the hairs as in other parts of the body. The addition of lysin alone to a dietary containing zein does not prevent the decline which always accompanies the taking of a diet which is free from tryptophan.

From the experiments of McCollum,[1] one may calculate that gelatin (which lacks tyrosin, tryptophan, and cystin), when given with starch to a pig in such quantity that the gelatin is the equivalent of the wear-and-tear quota of protein metabolism, body protein is protected from waste to an extent of 39 per cent. (see p. 225). When zein is administered under similar conditions body protein is spared to an extent of 73 per cent., thus demonstrating the superiority of zein to gelatin in this regard.

The study of the failure of zein to produce growth or to prevent decline brings up the question as to the nutritive value of maize. Osborne and Mendel[2] state that zein and glutelin form 72 per cent. of the proteins of the maize kernel. Glutelin, which is present in about one-half the quantity of that of zein, is a complete protein, containing all the familiar amino-acids, and is efficient in producing growth, but there is not enough of this higher quality protein to produce more than moderate growth. A small addition of a protein like lactalbumin, however, to a diet containing maize protein at once induced normal growth.

The corn (maize) grain contains little calcium, and the daily addition of 2.5 grams Ca to the diet of a corn-fed pregnant sow very favorably influences the condition of the offspring.[3] In experimental work upon vitamins and on the biological values of proteins, the ash content of the dietary must always be considered as a complicating factor.

Hart and McCollum[4] noticed that when swine are restricted to cornmeal and corn-gluten feed there is little or no growth, but when salts are added, so that the salt content of the ration approximates that of milk, good growth follows. The desire for salts may explain the "rooting" of the hog. The desirability of a milk addition to the diet of the growing hog is emphasized in the following experiment, which shows the higher biologic value of the milk proteins as contrasted with vegetable proteins. (See also p. 512.)

[1] McCollum, E. V.: Am. J. Physiol., 1911–12, **29**, 215.
[2] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1914, **18**, 1.
[3] Evvard, J. M., Dox, A. W., and Guernsey, S. C.: Am. J. Physiol., 1914, **34**, 312.
[4] Hart, E. B., and McCollum, E. V.: J. Biol. Chem., 1914, **19**, 373. Consult also Hogan, A. G.: *Ibid.*, **27**, 193.

EFFECT OF THE KIND OF PROTEIN UPON THE AMOUNT OF PROTEIN RETAINED FOR GROWTH

Source of Protein	Calories per Kg. in Ration	Protein in Per Cent. in Ration	Protein Retained for Growth in Per Cent.
Corn	109	10.5	20
Wheat	103	11.0	22
Oats	94	14.5	23
$\frac{1}{3}$ corn + $\frac{1}{3}$ wheat + $\frac{1}{3}$ oats	98	12.3	26
Wheat embryo + wheat gluten	98	57.9	21
Casein	102	16.5	46
Skim milk	94	15.5	63

When vegetable protein was administered in large quantity there was about the same percentage retention as when it was given in smaller amount. Hence, McCollum concludes that the limitation of growth when vegetable proteins are taken alone is due to the chemical make-up of these proteins and not to any diminution in the animal's power to grow.

The work of Osborne and Mendel upon the subject of the behavior of *gliadin*, one of the principal proteins derived from *wheat*, has been of very great interest. Gliadin is a protein which yields 44 per cent. of glutamic acid and 13 per cent. of prolin, these being present in exceptionally large quantities. On the other hand, it contains only 0.92 per cent. of lysin and very little arginin and histidin. When gliadin is the only protein in the diet grown rats may be maintained over long periods (546 days), but ungrown rats fail to grow,[1] although the gliadin administered is completely digested and absorbed. The animals remain stunted and resume growth only when an adequate protein in the diet is offered to them. Osborne and Mendel[2] have stunted albino rats until they were 550 days old, and then by a change of diet observed a resumption and completion of growth, although ordinarily such completion of growth is accomplished before the age of 300 days. It appears that if in these animals the function of growth has not been fulfilled at the usual period of life the capacity to grow is never lost.

If a diet be made up which contains gliadin as the dominant protein, and lysin be added so that the protein quota contains 2 or 3 per cent. of lysin, normal growth is resumed by a rat which had been stunted through the influence of the diet poor in lysin.[3]

[1] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1912, **12**, 473.
[2] Osborne, T. B., and Mendel, L. B.: *Ibid.*, 1915, **23**, 439.
[3] Osborne, T. B., and Mendel, L. B.: *Ibid.*, 1916, **25**, 1.

The principal proteins existing in wheat are gliadin and wheat *glutenin*, there being equal amounts of each. Since the latter form of protein completely suffices for the growth of rats, it is evident that

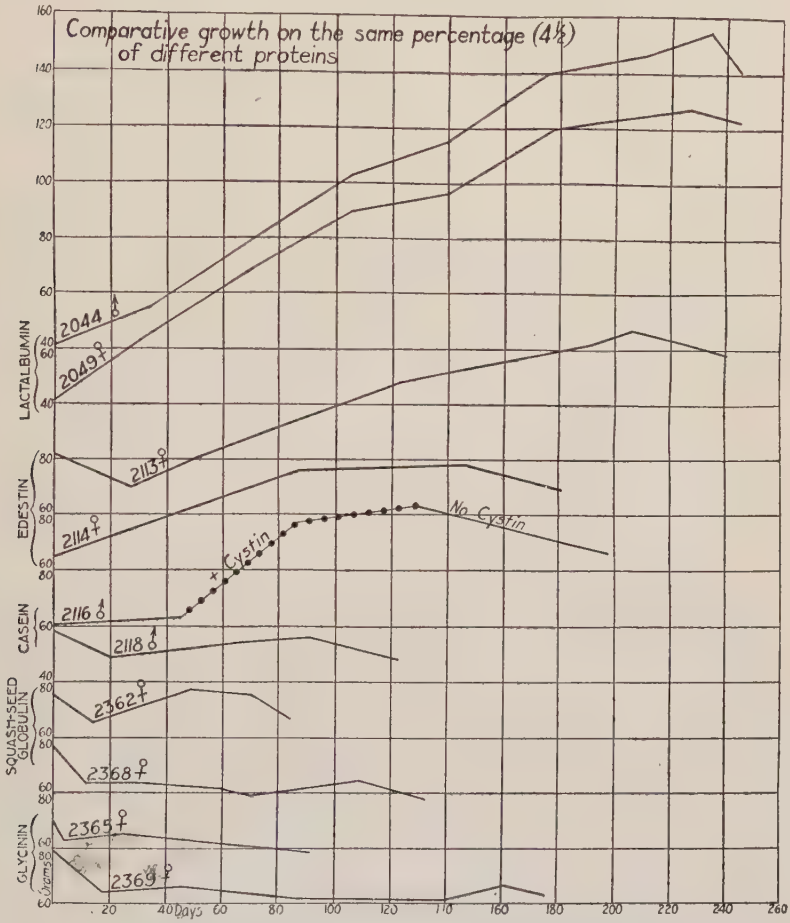


Fig. 29.—Comparison of growth on diets containing approximately the same percentage (4.5 per cent.) of different proteins, namely, *lactalbumin*, *edestin*, *casein*, *globulin* (squash-seed), and *glycinin* (soy bean).

the value of wheat protein is greatly enhanced by the presence of this constituent.

A notable contribution to the knowledge of the relative value of lactalbumin and casein has been presented by Osborne and Mendel.[1]

[1] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1915, **20**, 351; 1916, **26**, 1

It will be remembered that Thomas found that casein was inferior to milk protein for the maintenance of nitrogen equilibrium in man. The cause of the inferiority of casein is largely due to the fact that it contains only 0.6 per cent. of cystin (Fig. 29).

Mendel and Osborne found that when 3 per cent. of this latter amino-acid was added to the casein content of a diet, growth in the rat was accomplished with a much smaller quantity of protein than when casein alone was given. These results are presented in the following table:

INFLUENCE OF THE AMOUNT OF DIFFERENT VARIETIES OF MILK PROTEIN UPON THE GROWTH OF RATS

Percentage of Protein in the Diet	Casein	Casein + 3 Per Cent. Cystin	Lactalbumin
18	Normal.		Normal.
15	Normal.		Normal.
12	Little below normal.		Normal.
9	Limited.	Normal.	Normal.
6	Slight.	Good.	
$4\frac{1}{2}$	Maintenance.	Slight.	Limited.
2	Decline.		Maintenance.
1			Decline.

It is evident that a diet containing 15 per cent. of casein may be given to rats and produce normal growth, whereas when 12 per cent. is present normal growth does not take place. The addition of 3 per cent. of cystin to casein so that this mixture forms 9 per cent. of the diet yields a food capable of supporting normal growth. There is greater value in lactalbumin in promoting growth than in casein because the amino-acids are arranged in more suitable proportions. This protein of whey appears to be as perfect a material for use in the service of growth as any protein known.

Recent work of Osborne and Mendel[1] upholds all these important conclusions.

Confirmatory of the enriching physiological effect of small amounts of cystin upon proteins in the dietary is the work of Lewis,[2] whose experiments upon the nitrogen balances of dogs are here reported. The experiments represent the daily average of periods of 6 or 7 days.

[1] Osborne, T. B., and Mendel, L. B.: J. Biol. Chem., 1924, **59**, 339.
[2] Lewis, H. B.: *Ibid.*, 1927, **31**, 363; 1920, **42**, 289.

Daily Diet	N in Diet, Gm.	± N to Body, Gm.
Standard diet + 50 gm. meat	1.48	−1.21
" " + 50 " " + 1 gm. cystin	1.57	−0.37
" " + 50 " "	1.55	−0.78
" " + 50 " " + 1 gm. cystin	1.53	−0.18
" " + 50 " "	1.39	−0.49
" " + 10 " casein	1.77	−1.35
" " + 9.51 gm casein + 0.75 gm. cystin	1.77	−0.07
" " + 9.51 " " + 0.47 " glycin	1.77	−1.03
" " + 9.15 " " + 1.13 " tyrosin	1.77	−0.93
" " + 9.35 " " + 0.75 " cystin	1.77	+0.18

In no case did the addition of glycin, tyrosin, or phenylalanin improve the "biological value" of the protein tested in the striking manner that cystin was able to accomplish. Serum albumin of beef blood, which itself has a high content of cystin, is better able to establish nitrogen equilibrium than is casein unless the latter is supplemented by the addition of a little cystin, in which it is deficient. Upon such facts as these the differences in the biological values of different proteins are definitely established.

The following table, which is arranged from data given by Mendel,[1] presents the proteins with a supply of which an organism may grow, and also those which, if ingested, do not produce growth of the organism:

VALUE OF PROTEINS IN THE FUNCTION OF GROWTH

Allow Growth		Failure to Grow	
Casein	milk.	Legumelin	soy bean.
Lactalbumin	milk.	Vignin	vetch.
Ovalbumin	hen's egg.	Gliadin	wheat or rye.
Ovovitellin	hen's egg.	Legumin	pea.
Edestin	hemp-seed.	Legumin	vetch.
Globulin	squash-seed.	Hordein	barley.
Excelsin	Brazil-nut.	Conglutin	lupin.
Glutelin	maize.	Gelatin	horn.
Globulin	cotton-seed.	Zein	maize.
Glutenin	wheat.	Phaseolin	white kidney bean.
Glycinin	soy bean.		
Cannabin	hemp-seed.		

It is evident from the material presented in this chapter that the science of nutrition includes something more than the production of energy from fat, carbohydrate, and protein. There must be certain salts and certain qualities of protein in the diet, and there must be minute amounts of "vitamins." The chemical composition of the latter will some day be known, even as the chemical composition of epinephrin is known. Epinephrin, an essential of life, is present in the blood to the extent of 1 part in 100,000,000. In like manner,

[1] Mendel, L. B.: Harvey Society Lecture, J. Am. Med. Assn., 1915, **64**, 1539.

vitamins which are present in meat, milk, fresh green vegetables, and grains are essential to the harmonious correlation of the nutritive functions of animals. Lafayette Mendel first suggested the use of the word "hormone" in connection with the vitamins. Gowland Hopkins adopts the term "exogenous hormones." The expression "food hormones" would also be exactly descriptive of the nature of these substances.

CHAPTER XX

THE FOOD REQUIREMENT DURING THE PERIOD OF GROWTH

If we call the weight of the human egg one, then the weight of the individual produced from the egg is about sixteen billion times that of the egg itself.—G. H. PARKER.

"MUTE and still, by night and by day, labor goes on in the workshops of life. Here an animal grows, there a plant. The wonder of the work is not less in the smallest being than in the largest."[1]

In the last chapters the average food requirement of a normal adult organism has been discussed. This diet, however, may be exceeded in cases where there is a renewal of tissue following wasting disease, or where there is a development of new tissue, as during pregnancy, or afterward during lactation, which involves the growth of the newborn infant.

Tangl[2] has reported some interesting observations on the heat production which takes place in the hen's egg incubated at 38° and 39° F. Tangl called this the "energy for development" or the "ontogenetic energy." His method was to determine the calories in fresh laid eggs and to compare that amount with the calories found within the egg-shell at the moment of the birth of the chick. In this latter case the chick and the balance of egg-yolk were determined separately.

The results of these experiments showed that for the development of 1 gram of chick 658 small calories were used, or for the production of 1 gram of solids contained in a newborn chick 3425 small calories were required.

Farkas[3] has since shown that for the development from the egg of 1 gram of silkworm larvæ 882 small calories are required, or for 1 gram of dry solids, 3125 small calories, figures which he compares with Tangl's for the egg.

When the whole hen's egg is considered, Tangl finds that 32 calories or 35 per cent. of the amount of chemical energy in the

[1] Rubner, M.: Verhandl. Ges. deut. Naturforscher und Ärzte, 1909, p. 77.
[2] Tangl, F.: Pflüger's Arch. gesam. Physiol., 1902–03, **93**, 327.
[3] Farkas, K.: *Ibid.*, 1903, **98**, 490.

original egg is deposited in the body of the young embryo. The energy of development used in the production of the young chick amounts to 16 calories or 17 per cent. of the original total. The balance, 44 calories or 48 per cent. of the original energy in the egg, is largely found in the abdomen of the chick and is absorbed by the animal during the early days of life.

It is apparent from the above that approximately one-sixth of the energy in a hen's egg is used in the development of a chick whose body contains one-third the original energy of the egg. The other half of the energy becomes available for the chick during the first days of its separate life through absorption from the intestinal wall.

Tangl finds that each egg loses in solids during incubation, and that the heat value of 1 gram of such solids is over 9 calories. Since 1 gram of fat yields 9.3 calories, the natural inference is that fat furnishes the energy for development.

Hasselbalch[1] had formerly shown that the respiration carried on by an egg indicated a respiratory quotient amounting to 0.677. This low quotient points to the combustion of fat.

Tangl[2] also states that there is no loss of protein nitrogen by the egg during incubation, and that the egg-shell contributes to bone formation in the chick, losing 6.1 per cent. of its dried substance to this end.

Needham[3] states that during incubation the CO_2 output rises from 10 c.c. to 400 c.c. per 24 hours. Needham criticises the term "energy of ontogenesis" and believes that there is no energy required for development but only for the maintenance of the embryo. Murray[4] also has made a careful study of the metabolism of chicken embryos. During the last 5 days of incubation the metabolism amounts to four-fifths of that of the whole period and the respiratory quotient is 0.71, thus confirming Hasselbalch's conclusion that the energy is derived from fat. The metabolism per unit of weight of embryo is very high in the earlier days of incubation; on the 5th day the oxygen absorption is 50 c.c. per gram of wet weight of the embryo; 10th day 35 c.c.; 15th day 30.5 c.c.; and 19th day 20 c.c. Murray calculates that the food requirement of the embryo on the 6th day is

[1] Hasselbalch, K. A.: Skan. Arch. Physiol., 1900, **10**, 353.
[2] Tangl, F., and v. Mituch, A.: Pflüger's Arch. gesam. Physiol., 1907–08, **121**, 437; Tangl, F.: *Ibid.*, 423.
[3] Needham, J.: Physiol. Rev., 1925, **5**, 1.
[4] Murray, H. A., Jr.: J. Gen. Physiol., 1926–27, **10**, 337.

the equivalent of the energy content of the embryo itself. The metabolism is therefore relatively enormous.

Glaser[1] has found that the energy of ontogenesis for the eggs of fundulus is similar in quantity to that necessary for the hen's egg and for silkworm larvæ, and is also evolved at the expense of the oxidation of fat. He reiterates Tangl's statement that the specific energy of ontogenesis is not a function of phylogenetic position or of organization, but that the embryonic construction of different kinds of highly organized living forms may take place at the same expense of chemical energy.

Grafe[2] has stated that the isolated tissue of mouse, rat, guinea-pig, bird, cat, rabbit, dog, sheep, man, calf, and ox, used in respiration about 0.2 c.c. oxygen per gram of dry substance per minute. He found that isolated mouse tissue respired 1.7 times more oxygen than ox tissue. Since he knew that *in vivo* the metabolism of mouse tissue is 33.3 times that of ox tissue, he concluded that in the living ox inhibitory impulses were applied to the tissue reducing the intensity of its metabolism to one-twentieth of its possible value. After this fashion, he declared, the specific energy metabolism within the protoplasm of warm-blooded animals is essentially controlled by the law of surface area and is associated with the integrity of the living organism. The validity of this work has been denied by Wels,[3] who does not think that Grafe is right in believing that the tissues of animals of different sizes have the same metabolism. Thus Meyerhof and Himwich[4] found that the heat production of a mouse's diaphragm was twice as great as that of a rat. Wels gives the following values for the muscle tissue of different animals.

	O_2 in Cmm. Absorbed per Mg. Dry Muscle per Hr.
Young mouse	13.4
Adult mouse	10.6
Young rat	7.5
Adult rat	5.7
Young guinea-pig	5.1
Old guinea-pig	3.5

These results indicate that the respiratory activity is different in different types, the isolated muscles of the larger animals manifesting a decrease in the intensity of the metabolic process.

[1] Glaser, O. C.: Biochem. Z., 1912, **44**, 180.

[2] Grafe, E., Reinwein, H., and Singer: *Ibid.*, 1925, **165**, 102; Pflüger's Arch. gesam. Physiol., 1925, **209**, 781.

[3] Wels, P.: Pflüger's Arch. gesam. Physiol., 1925, **209**, 32.

[4] Meyerhof, O., and Himwich, H. E.: *Ibid.*, 1924, **205**, 415.

The trouble with Grafe's experiments lies in the technical difficulty of obtaining a normal oxygen supply in the isolated musculature of large animals.

Wels's experiments demonstrate that in mammals after birth, just as in the embryonic chick, the metabolism of the youthful protoplasm has a higher rate than that of the adult.

INFLUENCE OF THE SEX GLANDS UPON THE METABOLISM OF WOMEN

There is no great change in the intensity of the oxidation processes in women during menstruation, a fact first shown by L. Zuntz[1] and confirmed by Du Bois.[2]

Blunt and Dye[3] used as subjects seventeen women who were either members of a university faculty or were medical students and found that there was no change in basal metabolism due to menstruation.

Intermenstrual calories per 24 hours	1351
Menstrual " " 24 "	1328

The average difference was 1.7 per cent. The basal metabolism was −4.1 per cent. of the Harris-Benedict prediction tables and −6.5 per cent. of Du Bois' standards. Hafkesbring and Collett[4] find a definite tendency toward a rise in basal metabolism before each menstrual period and a sharp drop on the 1st and 2d days of menstruation, but the difference between the high and low points is only 5 per cent. and there is no change in the pulse rate. Wakeham[5] reports similar results.

Schrader[6] showed that there was a retention of protein nitrogen in six women either during the whole menstrual period or during the first part of it. This is in compensation for the loss of blood.

It is stated by Geist and Goldberger[7] that castration in women with previously functioning ovaries has no effect on basal metabolism, body weight, or blood chemistry.

"A direct influence of the sexual organs on metabolism does not exist" is the positive statement of Leon Asher.[8] This confirms the

[1] Zuntz, L.: Arch. f. Physiol., 1906, p. 393.
[2] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 907.
[3] Blunt, K., and Dye, M.: J. Biol. Chem., 1921, **47**, 69.
[4] Hafkesbring, R., and Collett, M. E.: Am. J. Physiol., 1924, **70**, 73.
[5] Wakeham, G.: J. Biol. Chem., 1923, **56**, 555.
[6] Schrader, T.: Z. klin. Med., 1894, **25**, 72.
[7] Geist, S. H., and Goldberger, M. A.: Am. J. Obstet. and Gynecol., 1926, **12**, 206.
[8] Asher, L., and Bertschi, B.: Biochem. Z., 1920, **106**, 37.

older experimental evidence of Lüthje[1] which showed that castration in dogs of both sexes had no influence on metabolism.

THE BASAL METABOLISM IN PREGNANCY

During pregnancy in the higher animals not only must there be growth of the breasts, of the uterine musculature, and of the embryo itself, but there must be energy expended in maintaining the new organism; hence the appetite of the mother increases during pregnancy. Magnus-Levy[2] finds an increased requirement for oxygen on the part of the mother as pregnancy progresses. His table is as follows:

	Oxygen in c.c. per Min.
Non-pregnant	302
Third month of pregnancy	320
Fourth " "	325
Fifth " "	340
Sixth " "	349
Seventh " "	348
Eighth " "	363
Ninth " "	383

Rubner[3] called attention to the fact that the mammalian embryo has no appreciable weight in relation to the mother until the middle of the gestation period, and, in fact, up to this time the metabolism of the mother is usually found to be unchanged.[4] At term, however, the weight of the child is between 5 and 6 per cent. that of the mother, and when the various adnexa are considered the mother loses during parturition the equivalent of nearly 20 per cent. of her postpartum weight.

Experiments which were carried out by Carpenter and Murlin[5] present an admirable picture of metabolism under the change in conditions effected by parturition. These authors investigated the heat production of three pregnant women in the "bed calorimeter" of the Carnegie Nutrition Laboratory and followed this with similar determinations upon the same women after parturition, each woman being placed in the calorimeter several times, alone and also with her offspring. Observations were made during one to three weeks preceding parturition and during about two weeks following the event.

[1] Lüthje, H.: Arch. exper. Path. u. Pharm., 1902, **48**, 184.

[2] Magnus-Levy, A.: Z. f. Geburtsh. u. Gynäk., 1904, **52**, 116. Also see Magnus-Levy, A.: von Noorden's "Handbuch des Stoffwechsels," Berlin, 2d ed., 1906, **1**, p. 409.

[3] Rubner, M.: Arch. f. Hyg., 1908, **66**, 177.

[4] Zuntz, L.: Ergeb. d. Physiol., 1908, **7**, 430; Arch. f. Gynäk., 1910, **90**, 452.

[5] Carpenter, T. M., and Murlin, J. R.: Arch. Int. Med., 1911, **7**, 184.

A summary of the results is presented in the following table.

METABOLISM BEFORE AND AFTER PARTURITION. THE METABOLISM OF THE CHILD WAS DETERMINED BY DIFFERENCE

	Weight in Kg.	Calories per Hour	Calories per Sq. M. (Meeh)	Calories per Kg. per Hour
Case I:				
Before parturition	63.0	60.7	31.4	0.96
After parturition	51.4	53.9	31.7	1.05
Difference	11.6	6.8		
Child	2.7	7.3	30.5	2.70
Case II:				
Before parturition	58.0	64.7	35.1	1.11
After parturition	48.5	59.0	36.2	1.21
Difference	9.5	5.7		
Child	3.4	9.8*	34.9	2.88
Case III:				
Before parturition	69.1	70.6	34.0	1.02
After parturition	60.1	60.4	31.9	1.00
Difference	9.0	10.2		
Child	3.2	9.3	34.8	2.90
Average:				
Before parturition	63.4	65.3	33.4	1.03
After parturition	53.3	57.8	33.2	1.09

* Child cried during the experiments.

In cases I and III the metabolism of the child alone was almost exactly equal to the decrease of the metabolism of the woman which ensued after parturition. The authors point out that during parturition the mother loses a considerable weight of material, such as liquor amnii, blood, membranes, placenta, etc., which themselves participate little or not at all in the production of heat. In the cases here cited the heat production of the newborn infant averages 2.6 times that of the mother when the calculation is based upon the calories produced per kilogram of body weight. It is probable, though not experimentally demonstrated, that the youthful, growing protoplasm *in utero* is also endowed with a high metabolism per kilogram of body weight. In the pregnant condition the average weight of these three women was 63 kilograms, and 33.4 calories were produced per square meter of surface. After parturition the average weight was 53 kilograms and the heat production 33.2 calories per square meter of surface. Using Meeh's formula, the average heat production of women between twenty and fifty years old, as determined by Benedict and Emmes,[1] is 32.3 calories per square meter of

[1] Benedict, F. G., and Emmes, L. E.: J. Biol. Chem., 1915, **20**, 253.

surface. Herein lies a most remarkable confirmation of the "law of skin area" (see p. 123). Notwithstanding a sudden loss of 10 kilograms, or nearly 20 per cent. of the final body weight, as well as the loss of tissues with very uneven capacities of heat production, the sum total of energy production is not altered by gestation or parturition from the common standard of mammalian metabolism as based upon the surface area.

The three mothers nursed their children throughout the days of experimentation. It appears that lactation does not increase the heat production. This is not strange, since the rearrangement of food materials in the preparation of milk depends upon hydrolytic cleavages and syntheses which involve hardly any thermal reactions, and also because it is known that the secretory activity of a gland, such as the kidney when it eliminates urea or sodium chlorid in increased quantity, has no influence upon the total heat production of the body.

The findings of Hasselbalch[1] are not essentially different from those of Carpenter and Murlin.

Excellent work by Root and Root[2] and Rowe, Alcott and Mortimer[3] should be read by those interested, but the most complete picture of metabolism in pregnancy is given by Sandiford and Wheeler,[4] and it is therefore here reproduced. The work concerns the fourth pregnancy of a woman 34 years of age.

THE BASAL METABOLISM BEFORE, DURING, AND AFTER PREGNANCY

1923–24	Weight	Calories		± Du Bois Standard	Condition
		Per Hour	Per Sq. M.		
	Kg.				
Feb. 27	62.7	55.7	34.0	− 7	
Mar. 3	....	....	....	....	Menses began.
Apr. 30	65.2	58.5	35.0	− 4	2 months.
May 28	66.1	54.5	32.3	−11	3 "
June 27	67.2	54.0	31.8	−12	4 "
July 25	67.5	56.1	33.0	− 9	5 "
Aug. 15	68.5	58.8	34.4	− 5	5.5 "
Oct. 31	74.9	67.9	38.3	+ 5	8 "
Nov. 30	76.3	70.2	39.0	+ 7	9 "
Dec. 7	77.1	70.9	39.4	+ 8	Day of confinement. Baby 3.6 kg.
" 12	67.5	59.7	35.2	− 3	Lactation.
Feb. 4	68.9	57.4	33.6	− 8	"

[1] Hasselbalch, K. A.: Skan. Arch. Physiol., 1912, **27,** 1.
[2] Root, H. F., and Root, H. K.: Arch. Int. Med., 1923, **32,** 411.
[3] Rowe, A. W., Alcott, M. D., and Mortimer, E.: Am. J. Physiol., 1924–25, **71,** 667.
[4] Sandiford, I., and Wheeler, T.: J. Biol. Chem., 1924–25, **62,** 329.

Fetal movements must have increased the metabolism during the last month.

The average basal heat production for 4 days before confinement was 70.4 cals.; for 3 days after confinement 61.6 cals. per hour. The difference is 8.8 cals. per hour, or 211 cals. in 24 hours. Since the fetus at birth had an area of 0.26 meter, the metabolism of the child *in utero* may be computed at 812 cals. per square meter of surface per day, which is in agreement with Talbot's standard of 650 to 800 cals. per square meter of surface for newborn children.

It appears to be quite certain that the greater part of the extra metabolism of the pregnant mother is due to the metabolism of the fetus itself.

Murlin[1] has made experiments on *the total metabolism in pregnant dogs*. From one animal a single puppy was born as the result of a first pregnancy and a litter of five from a later one. The following results were obtained:

Day from Parturition	Date	Excreta		Calories of Metabolism	
		Total N	Total C		
	1928	Gm.	Gm.		
Third before	June 23	8.6	59.4	551.3	One puppy born.
First after	June 27	8.4	65.8	640.6	Weight, 280 grams.
Nineteenth after	July 15	5.3	51.6	505.3	Sexual rest.
Third before	Dec. 11	6.8	74.7	764.9	Five puppies born.
First after	Dec. 15	8.3	100.6	1058.8	Weight, 1560 gms.

The increase of metabolism which can be attributed to the pregnant condition may be found by subtracting the metabolism during sexual rest from that observed just before parturition. By so doing the following figures were obtained:

First pregnancy, 551.3 − 505.3 = 46 calories daily for one puppy of 280 grams.
Second pregnancy, 764.9 − 505.3 = 259.6 calories daily for five puppies of 1560 grams.

This extra metabolism was proportional to the weight of the puppies at birth. In the case of the first pregnancy the extra metabolism was 164, and in the second 165 calories per kilogram of puppy dog delivered three days later.

[1] Murlin, J. R.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1908–09, **23**, p. xxxii.

It is interesting to note that the mother and her five newly born puppies together produced twice as much heat as did the non-pregnant mother alone. The experiments were all made at a temperature of between 27° and 28° C. It is evident that the puppies suckled by the mother and exposed to the outside temperature had a larger metabolism than they had had *in utero*. For the proper maintenance of the five offspring the mother with a normal metabolism of 505 calories would have to produce milk to provide for a metabolism of about 550 calories in the puppies, and still more to furnish material for their rapid growth.

Ostertag and Zuntz[1] report that a sow may yield a milk rich in fat (12.9 per cent.), and in such quantity that the energy content may amount to from two- to fivefold that required for the mother sow's metabolism.

PROTEIN METABOLISM IN PREGNANCY

An extraordinary phenomenon which has been observed in dogs and rabbits is that during the early weeks of pregnancy there is a loss of nitrogen from the mother's body even when the food ingested would be entirely sufficient to maintain nitrogen equilibrium under usual circumstances.[2] Jägerroos quotes Ver Ecke's description of this as "the sacrifice of the individual for the good of the species." It seems certain that the development of the fetus is accompanied by the destruction of the maternal protoplasm, perhaps, as Murlin has suggested, in order to afford hereditary building stones for the laying down of the youthful protoplasm in accordance with the type characteristic of the species.

This is the period of the "morning sickness," established in pregnant women during the fourth to sixth week, and accompanied by lack of appetite, vomiting, emaciation, and usually sallowness of face. Dissimilation of tissue and gastro-intestinal disturbances are accompanying phenomena.

One of Murlin's[3] experiments covering the period of gestation in a dog is given below:

[1] Ostertag, R., and Zuntz, N.: Landwirtsch.Jahrbücher, 1908, **37**, 226.
[2] Hagemann, O.: Inaugural Dissertation, Berlin and Erlangen, 1891; Jägerroos, B. H.: Arch. f. Gynäkol., 1902, **67**, 517.
[3] Murlin, J. R.: Am. J. Physiol., 1910–11, **27**, 177.

WEEKLY NITROGEN BALANCE IN A PREGNANT DOG

Week	Calories in Food per Day	N in Diet, Gm.	N in Excreta, Gm.	N to Body, Gm.
I	900	53.287	63.116	−8.83
II	976†	56.063	60.893	−4.83
III	976	56.063	62.031	−5.97
IV	976	56.063	64.508	−8.44
V	976	56.063	62.594	−6.53
VI	976	56.063	60.064	−4.00
VII	976	56.063	54.262	+1.80
VIII	976	56.063	47.042	+9.02
IX*	976‡	32.036	25.867	+6.25

* Four days only.
† 72 calories per kilogram.
‡ 61.0 calories per kilogram.

This shows the large loss of maternal protein commencing immediately after conception and continuing for six weeks. Only during the last two weeks is there a marked conservation of protein as manifested in the pronounced nitrogen retention.

Some very instructive experiments have been performed to ascertain the course of the protein metabolism before and after pregnancy in women.

Zacharjewski[1] investigated the nitrogen metabolism of 9 pregnant women. In 3 primiparæ, nourished on diets containing an average of 16.5 grams of nitrogen, there was an average daily retention of 1.4 grams in the mother's organism for thirteen days before parturition. In 6 multiparæ the diet contained 20.6 grams of nitrogen, and there was a daily retention of 5.12 grams of nitrogen during the last eighteen days of pregnancy. The figures correspond to a considerable construction of protein tissue within the organism. After childbirth there was always a loss of tissue nitrogen by the mother. In one case nitrogen equilibrium was established on the fifth day, and in another on the fourth. In 6 cases the loss of body nitrogen continued over a longer time. Zacharjewski says that the process of involution of the uterus is greatest during the first five to seven days after delivery, and the high nitrogen output from the mother is the result of this. After the elimination which is due to these regressive changes there is a retention of nitrogen. This is probably attributable to the building up of the mammary glands, for Slemons[2] shows that nitro-

[1] Zacharjewski, A. U.: Z. f. Biol., 1894, **30**, 405.
[2] Slemons, J. M.: Johns Hopkins Hosp. Rep., 1904, **12**, 121.

gen equilibrium, once established, was constantly maintained in a woman who did not nurse her child.

The complete record of the nitrogen elimination of a nursing mother, one of Slemons' cases, is here reproduced. It is especially instructive on account of the constancy of the quantity of nitrogen in the diet. The woman was a negress who gave birth to a healthy, vigorous child.

PROTEIN METABOLISM BEFORE AND AFTER CHILDBIRTH
(Weights are in grams)

Days before and after Delivery	N in Food	N in Urine	N in Feces	N in Milk	N in Lochia	N Balance
11	20.5	11.9		....	....	+8.12
10	19.2	16.6		....	....	+2.07
9	18.0	10.9		....	....	+6.57
8	16.9	17.1		....	....	−0.77
7	11.3	13.7		....	....	−2.95
6	19.2	13.3	0.53	....	....	+5.39
5	19.2	12.1		....	....	+6.57
4	19.2	14.1		....	....	+4.54
3	18.0	12.3		....	....	+5.12
2	14.9	12.3		....	....	+2.06
1	8.0	11.5		....	....	−4.00
Delivery	4.2	8.4		....	3.15	
1	7.1	13.3		....	2.31	−9.66
2	13.7	13.2		0.15	1.99	−2.79
3	19.0	15.8		1.04	1.61	−0.57
4	19.0	18.8	1.14	1.99	1.19	−4.13
5	20.0	15.6		2.02	1.05	+0.15
6	20.0	21.8		2.15	1.4	−6.5
7	19.0	18.1		2.02	0.84	−3.14
8	11.0	16.8		2.02	0.28	−9.2
19	19.8	12.1		1.18	....	+4.89
20	18.8	15.3		1.29	....	+0.57
21	19.9	13.3		1.57	....	+3.39
22	17.3	9.7	1.6	1.58	....	+4.39
23	18.0	13.9		1.85	....	+0.68
24	18.75	11.4		2.03	....	+3.72
25	19.0	15.6		1.58	....	−0.16

During the last days of pregnancy there was an average daily storage of 2.98 grams of nitrogen, and for eight days of the puerperium an average loss of 4.5 grams. Later, between the nineteenth and twenty-fifth days after parturition, there was an average daily storage of 2.52 grams of nitrogen. This may have been for the purpose of increasing the size of the breasts. It must be remembered that even during the period of involution an increase in the mammary glands may have been taking place at the expense of protein derived

from the uterus. So the debit balance of nitrogen during this period may not represent all the protein change taking place.

The composition of the urine, as regards its various constituents, is scarcely changed in pregnancy. Thus, Murlin and Bailey[1] found that the output of ammonia was not increased, that the relative quantity of urea decreased because of protein retention, and that the quantity of oxidized inorganic sulphur also decreased for the same reason, retention for protein synthesis. The "creatinin coefficient" fell, which the authors explain as being due to the addition of inert material to the mother's body.

The high ammonia found by others in eclampsia was shown by Murlin and Bailey to be due to bacterial fermentation of the urine.

GROWTH OF THE FETUS

An elaborate experiment upon the subject of the metabolism of the pregnant woman was carried out by Hoffström,[2] and extended over the period of the last twenty-three weeks of pregnancy. He computes the probable composition of the ovum at the end of the sixteenth week and compares that with the estimated composition of the child at birth, and also computes the constituents of the food retained for the growth of the child and the mother:

	Retained from Food during Twenty-three Weeks			Composition of Ovum, Sixteenth Week
	Total	For Mother	For Fetus	
	Grams	Grams	Grams	Grams
N	310.05	208.57	101.48	4.28
P	55.88	34.0	18.0	0.67
Ca	34.31	4.2	30.12	0.38
Mg	2.44	1.46	0.98	0.026

There was an irregular retention of magnesium. Rapid growth of the fetus began during the twenty-ninth week of pregnancy, at which time the calcium retention by the organism greatly increased and the excretion of calcium in the feces of the mother diminished. The retention of materials by the mother herself represents the requirement for the growth of the uterus, the breasts, the gluteal and leg muscles.

[1] Murlin, J. R., and Bailey, H. C.: Arch. Int. Med., 1913, **12**, 288.
[2] Hoffström, K. A.: Skan. Arch. Physiol., 1910, **23**, 326.

Hoffström gives the following computation of the growth of the fetus:

GROWTH OF THE HUMAN FETUS COMPUTED FROM THE TABLES OF MICHEL

(Values in grams)

Week of Pregnancy	N		P		Ca		Mg	
	Content of Ovum	Added per Week	Content of Ovum	Added per Week	Content of Ovum	Added per Week	Content of Ovum	Added per Week
16	4.28	1.13	0.67	0.20	0.38	0.41	0.026	0.017
20	8.81	....	1.47	....	2.03	....	0.095	
21	.....	1.81	.....	0.25	.....	0.43	.....	0.017
28	23.28	....	3.58	....	5.39	....	0.234	
29	.....	6.87	.....	1.28	.....	2.09	.....	0.064
40	105.76	6.87	18.93	1.28	30.51	2.09	1.004	0.064

It is obvious that during the last ten weeks of pregnancy a diet which is rich in calcium is indicated or there may be a withdrawal of calcium from the mother's bones. Cows' milk contains much calcium and is a highly desirable addition to the dietary of the pregnant woman. (See p. 517.)

On empirical grounds von Winckel[1] for many years used the following diet for pregnant women with, he says, "excellent results:"

Protein	90 grams.	369 calories.
Fat	27 "	251 "
Carbohydrates	200 "	820 "
Total		1440 "

This certainly seems a very low ration and one hardly compatible with furnishing the full calorific requirement. It was employed to prevent an excessive growth of the child within the uterus.

THE PRODUCTION OF MILK

The mother, previously described as having been investigated by Slemons, had plenty of milk, and the baby gained an average of 30 grams a day during the first forty days of his life.

Slemons remarks that the low protein metabolism, as indicated by the urinary nitrogen of the period of settled lactation, is a proof that there can be no important production of milk fat from protein.

In the experiment cited it will be noticed that the nitrogen of the milk is small in quantity as compared with the urinary nitrogen.

[1] von Winckel, F.: E. von Leyden's "Handbuch der Ernährungstherapie," Leipzig, 2d ed., 1904, 2, p. 469.

On a strictly vegetarian diet the relation would change. Thus Voit[1] found 48.8 grams of nitrogen in the milk of a cow and 93.7 grams of nitrogen in her urine for the same period.

The influence of nutrition on the production of milk has been the object of countless investigations, but unfortunately most of these experiments have been conducted for commercial purposes on cows and goats. These animals, with their fundamental ration consisting of hay, do not allow of the ingestion of simple foods. On the other hand, the milk supply of even a large bitch is very limited in quantity and is with difficulty obtained.

In Detroit, in connection with the Woman's Hospital and Infants' Home, Hoobler[2] collected and distributed over 650 liters of human milk in 6 months to babies in need of it. If a mother developed a good milk producing capacity, that is, 450 to 675 c.c. above that needed by her own baby, she was urged to continue high milk production as a means of earning her living. The influence of various diets was investigated in 4 to 7 day periods. The largest volume of milk was obtained from a diet containing nuts, vegetables, cereals, and fruits. Thus in one instance the mother produced 1758 c.c. of milk, containing 1096 calories, when the diet of the period contained 2670 calories in the above named ingredients. This diet, however, caused a severe drain on the protein resources of the mother's body, and hence animal protein in the form of cow's milk or of meat was added to the diet of the nursing mother. When a diet contained meat, cereals, milk, vegetables, and eggs, and 2774 calories, the milk production was 1521 c.c., containing 1269 calories. Evidently conditions exist in the mother under which a large proportion of the diet may be converted into nutriment for the offspring.

A valuable research is an old one of Voit[3] upon a bitch weighing 34 kilograms. It confirmed the previous work of Kemmerich and of Ssubotin, and has since been verified by Grimmer.[4] The animal was given meat alone, meat and starch, meat and fat, starch alone, fat alone, and was also starved. The influence upon the milk secretion was found to be comparatively small. The research is a model of completeness, the plan of which was in part copied in the experiments on human beings by Hoobler.

[1] Voit, C.: Z. f. Biol., 1869, **5**, 122.
[2] Hoobler, B. R.: Am. J. Dis. Child., 1917, **14**, 105; J. Am. Med. Assn., 1917, **69**, 421.
[3] Voit, C.: Z. J. Biol., 1869, **5**, 137.
[4] Grimmer, W.: Biochem. Z., 1915, **68**, 311.

A part of the results are given below.

INFLUENCE OF DIET ON THE COMPOSITION OF THE MILK OF A DOG WEIGHING 34 KILOGRAMS

	Food			Milk						
Day	Meat, Grams	Other Food, Grams	N, Grams	Amount C.C.	N, Grams	Fat, Grams	Sugar, Grams	Protein, Per Cent.	Fat, Per Cent.	Sugar, Per Cent.
6.....	1000	300 starch	34	115	1.1	8.8	3.1	5.97	7.70	2.71
7.....	1000	200 fat	34	144	1.4	10.8	3.8	6.86	7.50	2.67
8.....	1000	200 fat	34	135	1.1	11.3	2.9	6.22	8.39	2.15
9.....	Mixed diet	.....	..	151	1.4	13.9	3.4	6.37	9.22	2.24
10.....	500	400 starch	17	138	1.2	11.3	3.8	5.83	8.19	2.78
11.....	500	300 fat	17	168	1.6	16.5	4.2	6.06	9.83	2.52
12.....	Starv.	.....	..	149	1.5	13.8	3.9	6.36	9.24	2.65
13.....	Starv.	.....	..	118	1.0	12.2	3.0	5.62	10.32	2.58
14.....	.....	500 starch	..	137	1.1	10.1	4.3	5.41	7.39	3.11
16.....	2000	.....	68	158	1.6	16.1	4.4	6.68	10.17	2.82
17.....	2000	.....	68	161	1.7	14.7	4.7	6.78	9.11	2.91

The largest quantity of milk, as well as the richest in protein, was obtained when meat or meat and fat were ingested. Curiously enough, a diet of 500 grams of meat and 300 grams of fat gave milk of the same amount and quality as did 2000 grams of meat. It is usually said that a large protein diet stimulates the milk secretion; but this may also be due indirectly to the development of the gland cells.

The milk-sugar content was scarcely affected by the diet, although a slight percentage increase was observed after starch ingestion.

The fat content was increased in starvation to its highest percentage. It was not very greatly affected by adding fat to a meat diet and it was greatly reduced by giving carbohydrates.

The action of fasting on the fat content of milk is better shown in the herbivorous goat. The writer[1] gave a milch goat a constant diet of hay, cornmeal, and bran, starved the animal for two days, and then continued the former diet. The fat content of the milk was determined. The results were as follows:

Milk in C.C.	Fat in G.	Fat in Per Cent.	
460	26.50	5.76	
470	25.90	5.52	
383	23.90	6.23	Starvation.
198	18.35	9.27	Starvation.
232	18.75	8.08	
298	16.30	5.47	
348	14.04	5.61	
362	22.30	6.16	
490	27.70	5.66	

[1] Lusk, G.: Z. f. Biol., 1901, **42**, 42.

In fasting, therefore, the fat content in the milk of the herbivorous goat approaches that contained in the carnivorous dog. With a return to the normal diet the fat content in goats' milk is reduced to its former level.

Morgen, Beger, and Fingerling[1] find that a diet rich in carbohydrate and poor in fat produces in sheep and goats a poor milk containing little fat, although the general condition of the animals remains perfect. Addition of protein increases the quantity of the milk without changing the low fat percentage. Replacement of some of the carbohydrate with isodynamic quantities of fat, up to 0.5 to 1.0 gram per kilogram of animal, largely increases the fat content of the milk and thereby its nutritive value.

Contrary to this is Jordan's[2] statement that the amount of fat in the fodder is without influence upon the fat content of a cow's milk. Here the breed of the cow and not the diet is the determining factor. The German agricultural stations have also reached the same conclusion. Morgen[3] states that the principal cause of the difference in the results of the experiments on cows and on sheep and goats lies in the fact that the smaller animals produce more milk for their weight than do cows, and, therefore, the milk production is much more dependent on the food supply.

The work of Prausnitz[4] indicates that although food does not determine the quantity of protein, lactose, or ash in cow's milk, yet the percentage of fat, and hence the caloric value of the liter of milk, may be considerably influenced by variations in the diet.

It has long been known that ingested fat may appear in the milk of an animal. Gogitidse[5] has shown that after sheep have taken linseed oil their milk fat may contain 33 per cent. of linseed oil. He also finds[6] that the fat of linseed oil passes readily into human milk, and that the fat of hemp-seed, while influencing the composition of the milk, greatly depresses lactation during the period of its ingestion.

Milk Production in Cows.—By breeding from pedigrees the old-fashioned cow of 40 years ago which yielded the farmer 1000 kg. of milk per annum has been supplanted by the present day average

[1] Morgen, A., Beger, C., and Fingerling, G.: Landw. Vers. Stat., 1904, **61**, 1.
[2] Jordan, W. H., and Jenter, C. G.: N. Y. Agri. Exp. Sta., Geneva, Bull. 132, 1897; Bull. 197, 1901.
[3] Morgen, A., Beger, C., Fingerling, G., and Westhausser, F.: Landw. Vers. Stat., 1908, **69**, 295.
[4] Helle, K., Müller, P. T., Prausnitz, W., and Poda, H.: Z. f. Biol., 1912, **58**, 355.
[5] Gogitidse, S.: *Ibid.*, 1904, **45**, 365.
[6] Gogitidse, S.: *Ibid.*, 1905, **46**, 403.

cow which yields twice that amount. The best herds now yield 3500 to 5500 kg. of milk per cow annually. Fries, Braman, and Cochrane[1] strike the following balance which shows the utilization of energy for milk production in one of their cows the metabolism of which was determined in the animal calorimeter of Armsby.

METABOLISM IN CALORIES OF A MILCH COW

	Intake	Outgo
Feed	32,462.6	
Feces		10,820.6
Urine		1,583.8
Methane		2,628.0
Brushings		110.1
Milk		5,378.2
Body protein	136.8	
Body fat		358.2
Balance		11,720.5
	32,599.4	32,599.4

The heat production of the cow, therefore, was 11,721 calories computed by the indirect method and it was 11,464 calories as measured by the calorimeter. The indirect computation was 102.2 per cent. of the heat directly measured. Milk containing 5378 calories was made at an expense of 11,721 calories of metabolism. The energy of maintenance included a 30 per cent. increase in metabolism during those parts of the day when the cow was standing above the level of the periods when the animal was lying. Milk containing 47 per cent. of the energy necessary for maintenance was therefore produced by this cow. Compare this with the ability of the resting hog to make 135 calories of fat from starch at the expense of metabolism in the beast equivalent to 100 calories derived from the starch. And then consider the difference between lard, which is nearly free from vitamin, and milk, with its many vitamins, its appetizing butter fat, its excellent proteins, its wide array of salts, and truly the culture of dairy products should be satisfying to the soul of man.

In an experiment upon Cow 221G the same authors[2] have shown that when the total heat production was 100 calories, the heat value of the milk reached 64.8 calories. Dr. Forbes writes of this work that none of these cows was a very extensive milk producer, that very high milk producers yield several times as much milk as those investigated at the Institute of Animal Nutrition, and that they have no

[1] Fries, J. A., Braman, W. W., and Cochrane, D. C.: U. S. Dept. Agricul. Bull. 1281, 1924, 1–36.

[2] Forbes, E. B., Fries, J. A., Braman, W. W., and Kriss, M.: J. Agricul. Research, 1926, **33**, 483.

record of the heat production of these high producers. The economic value of this knowledge would seem to be of great importance. Further details transcend the space limitations of this book.

Hart and Humphrey[1] have shown that the protein content of the milk varies very little even though a cow may be losing her own flesh to furnish the milk. Thus, when a cow received a food with a "nutritive ratio" of 1:8, that is, 1 part of protein to 8 parts of carbohydrate and fat, a positive nitrogen balance was present provided milk protein was given in the diet, but when protein was administered in the biologically lower form of wheat protein, a negative nitrogen balance resulted. The quantity of protein in the milk, however, remained unchanged.

These facts are shown in the following table:

	N Intake per Week, Grams	Fecal N, Grams	Absorbed N, Grams	Urine N, Grams	Milk N, Grams	Balance N, Grams
Wheat ration.....	953	404	549	464	227	−142
Milk ration.....	968	350	618	286	220	+112

"Milking the flesh off the back" is, therefore, a reality. During lactation a ration high in protein is wisely dictated and the biologic status of the protein must also be considered.

Harding and Montgomery[2] show that when the dietary of nursing women contains between 5 to 7.8 gm. nitrogen, even though 4000 calories be ingested in the food, body protein will be drawn upon to provide for the proteins of the milk.

According to similar laws, Fingerling[3] finds that a fodder deficient in calcium has no effect upon the calcium content of the milk, the organism providing this material. Furthermore, Lauder and Fagan[4] found that the addition of 225 grams of calcium phosphate to a fodder already containing the same content of that salt did not alter the calcium content of cows' milk. Von Wendt[5] states that ingestion with the fodder of sodium chlorid, calcium carbonate, calcium hydrogen phosphate, calcium glycerophosphate, sodium phosphate, or magnesium bromid is without definite influence upon the composition of the milk. The lactic glands, therefore, prepare a fluid of very definite composition specifically designed for the offspring of the species.

[1] Hart, E. B., and Humphrey, G. C.: J. Biol. Chem., 1915, **21**, 239.
[2] Harding, V. J., and Montgomery, R. C.: *Ibid.*, 1927, **73**, 27.
[3] Fingerling, G.: Landw. Versuchs. Stat., 1911, **75**, 1.
[4] Lauder, A., and Fagan, T. W.: Proc. Roy. Soc. Edinburgh, 1914–15, **35**, 195.
[5] von Wendt, G.: Skan. Arch. Physiol., 1909, **21**, 89.

The results obtained by Hart, Steenbock, Scott, and Humphrey[1] indicate that in cows with large milk yields receiving rations of grains, grain by-products, corn silage, and green grasses, calcium equilibrium can be obtained only when the ration is supplemented with lime. The diet contained 70 to 80 gm. calcium oxid and had to be supplemented by the addition of calcium carbonate to raise the total calcium oxid to 200 gm. per day. When green grasses, cut between 1 and 5 p.m. were fed to the cow, sunlight was not necessary. The picture of one of the experiments may thus be presented:

CALCIUM BALANCE AND MILK PRODUCTION IN A COW, PER WEEK

Green Grass	CaO Excretion				CaO in Food	CaO Balance	Milk
	In Feces	In Milk	In Urine	Total			
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Kg.
No sunlight	1084	229	27	1340	1394	+54	136
Sunlight	1055	239	22	1316	1363	+47	135

According to the latest announcement of Hart, Steenbock, and Scott[2] sunlight has no effect on the milk production of the cow, which contrasts with its influence on man, goat, and other animals. But Boas and Chick[3] and Luce[4] find that the antirachitic factor in the milk of cows, pasture fed in the sunshine, is at a maximum. The subject of the vitamin content of milk has been dealt with in the preceding chapter.

A complete analysis of the mineral balance of a milch cow, made early in lactation when the animal yielded 23.15 kg. milk and was on a diet of red clover, hay, grain, oats, vetch, silage, and kale, has been made by Miller, Yates, Jones, and Brandt.[5] Kale was given on account of its calcium content.

AVERAGE DAILY MINERAL BALANCE OF A COW RECORDED IN GMS.

	N	S	P	Cl	Ca	Mg	K	Na
Feed	315.6	33.5	58.5	72.9	117.0	45.0	226.4	43.1
Milk	109.7	6.4	22.3	17.7	27.3	2.8	28.0	8.1
Urine	115.7	9.7	0.7	38.0	0.8	8.5	178.8	16.7
Feces	108.7	12.0	36.7	18.3	95.1	36.0	17.1	4.9
Balance	−18.5	+5.4	−1.2	−1.1	−6.2	−2.3	+2.5	+13.4

[1] Hart, E. B., Steenbock, H., Scott, H., and Humphrey, G. C.: J. Biol. Chem., 1926–27, **71**, 263.

[2] Hart, E. B., Steenbock, H., and Scott, H.: *Ibid.*, 1927, **73**, 59.

[3] Boas, M. A., and Chick, H.: Biochem. J., 1924, **18**, 433.

[4] Luce, E. M.: *Ibid.*, 1924, **18**, 716, 1279.

[5] Miller, H. G., Yates, W. W., Jones, R. C., and Brandt, P. M.: Am. J. Physiol., 1925–26, **75**, 696.

THEORY OF MILK PRODUCTION

How may the various effects of diet be explained? The subject requires a knowledge of the processes going on in the mammary gland, and these are not certainly known. It has been generally believed that the cells of the mammary glands undergo a fatty metamorphosis and, themselves breaking up, pass into the milk (Voit, Heidenhain). The milk under these circumstances might be regarded as the substance of an organ, made fluid.

Schäfer,[1] however, believes the process to be one of secretion similar to that in the salivary glands, where the cells prepare the special constituents and pass them on to the lumen. Thus casein, like ptyalin, may be specially elaborated within gland cells.

If this be the true explanation, the influence of food, in the writer's opinion, may be readily explained. An increased protein ingestion furnishes the digestive products of this substance in liberal quantities and may increase the activity of the gland.

The milk-sugar content of the milk remains remarkably constant. Cremer,[2] for example, has shown that the percentage of milk-sugar in the milk is unchanged in the cow after diminishing the sugar content of the animal by inducing phlorhizin diabetes.

To explain the fat content of the milk the writer offers the following theory: When for any reason sufficient sugar is not oxidized in the body cells, these sugar-hungry cells attract fat. It has already been seen that the glycogen and fat content of the liver are antagonistic. Before lactation sets in, the cells of the mammary glands oxidize sugar and there is no great attraction for fat. It is believed that milk-sugar cannot be formed in any great quantity before parturition, because it occurs in the urine only *postpartum*.[3] That milk-sugar is not formed outside of the mammary glands was demonstrated by Moore and Parker,[4] who completely removed these glands from a goat during the period of gestation, and later at the time of parturition found no sugar in the urine. Had milk-sugar, which cannot be oxidized by the organism, been formed outside the glands it would have accumulated in the blood and have been eliminated in the urine. When in the process of lactation the glucose furnished by the blood is converted into milk-sugar (which cannot be burned within the

[1] Schäfer, E. A.: "Text-book of Physiology," Edinburgh and London, 1898, **1**, p. 667.
[2] Cremer, M.: Z. f. Biol., 1899, **37**, 78.
[3] Lemaire, F. A.: Z. physiol. Chem., 1895–96, **21**, 442.
[4] Moore, B., and Parker, W. H.: Am. J. Physiol., 1900, **4**, 239.

organism), the mammary cell becomes a sugar-hungry cell which at once attracts fat from the blood. This theory of the writer explains the production of milk fat by the process of infiltration. The variation of the percentage of fat in the milk may be explained by the quantity of fat in the blood. During starvation the blood becomes rich in fat on account of the transportation of tissue fat to the cells. Administration of sugar at once reduces the supply of fat in the blood. But if fat be ingested with carbohydrates the blood becomes rich with this fat and affords material for a rich milk.

The attraction of the lactic glands for blood sugar is illustrated by the statement of Carlens and Krestownikoff[1] that in the process of milking by machinery the blood sugar of a good milch cow may be reduced from 0.07 to 0.044 per cent.

Administration of good cream with a substantial mixed diet is highly to be recommended for nursing mothers. The daily production of a liter of milk, which has a value of 640 calories, indicates the necessity of no small addition to the daily ration, if the woman is to bear satisfactorily the strain of lactation. Probably this extra nourishment is best given in the form of fat.

Should the fat of the milk disagree with the infant, the trouble may be due to the kind of fat ingested by the mother. If, however, the indigestion be due to a large percentage of fat, a carbohydrate diet may be used to reduce the percentage in the milk.

Macy, Outhouse, Graham, and Long[2] find ample vitamin A in human milk, 2 to 2.5 c.c. of the milk of a wet nurse being sufficient to furnish enough vitamin A for the growth and reproduction of a rat. However, the same authors find that human milk is very poor in vitamin B, between 25 and 35 c.c. being needed to maintain a rat. In consequence of this other foods bearing vitamin B, such as orange juice, tomato juice, and later spinach, are early needed by the nursing infant. (For vitamin C, see p. 503; vitamin D, p. 504.)

Human milk has a varying calorific value dependent largely on the amount of fat present. Thus Schlossmann[3] finds that the calorific value per liter of nineteen samples of milk from 19 women averages 719 calories, with a maximum of 876 and a minimum of 567. The milks having the largest fuel value contained 5.2 to 5.1

[1] Carlens, O., and Krestownikoff, A.: Biochem. Z., 1927, **181**, 176.

[2] Macy, I. G., Outhouse, J., Graham, A., and Long, M. L.: J. Biol. Chem., 1927, **73**, 175, 189; Outhouse, J., Macy, I. G., Brekke, V., and Graham, A.: *Ibid.*, p. 203.

[3] Schlossmann, A.: Z. physiol. Chem., 1902–1903, **37**, 340.

per cent. of fat, while that having the lowest contained only 1.8 per cent.

It may be added that Völtz and Paechtner[1] report that after moderate ingestion of alcohol only minimal quantities of it are found in human milk.

MILK AS FOOD

A very important fact regarding the nutrition of the young is that the milk of one race is specifically adapted to the growth of the offspring of that particular race. Bunge[2] found that dogs' milk had an ash of exactly the same composition as the ash of the newborn puppy. The ash of the milk was, therefore, perfectly adapted for the construction of new puppy tissue. It was, however, very different in composition from human, or cows', or other milk. Only in the case of iron is the quantity lower than corresponds to the composition of the offspring, but this factor is offset by the fact that the animal when newborn is richer in iron than it is at any other period of life. Not only this, but the caseins of different milks are different in chemical behavior. And besides this, the rennin of the stomach is said to be specifically adapted for the coagulation of the casein produced by the female of the same race.[3]

Furthermore, the percentage quantity of the constituents in the milk is dependent upon the rapidity of the growth of the organism. Bunge[4] has shown this in the following comparative table:

	Time in Days for the Newborn Animal to Double Its Weight	100 Parts of Milk Contain		
		Protein	Ash	Calcium Oxid
Man	180	1.6	0.2	0.328
Horse	60	2.0	0.4	0.124
Calf	47	3.5	0.7	0.160
Kid	19	4.3	0.8	0.210
Pig	18	5.9		
Lamb	10	6.5	0.9	0.272
Dog	8	7.1	1.3	0.453
Cat	7	9.5		

Camerer[5] finds that human milk, drawn three to twelve days after parturition, contains 0.2 milligram of iron (Fe_2O_3) per 100 c.c., while the later milk contains 0.1 milligram. The quantity is

[1] Völtz, W., and Paechtner, J.: Biochem. Z., 1913, **52**, 73.
[2] Bunge, G.: Z. f. Biol., 1874, **10**, 326.
[3] Kiesel, K.: Pflüger's Arch. gesam. Physiol., 1905, **108**, 343.
[4] Bunge, G.: "Lehrbuch der physiologischen Chemie," Leipzig, 4th ed., 1898, p. 118.
[5] Camerer, W.: Z. f. Biol., 1905, **46**, 371.

decreased if the environment or the condition of the mother be poor.[1] Edelstein and Csonka[2] state that 1 liter of cows' milk contains 0.7 milligram of Fe_2O_3 (0.6 to 1 mg.), which is one-third to one-half the quantity contained in human milk. Using the customary methods of infant feeding with cows' milk, the infant obtains too little iron.

The addition of iron to the diet will not increase the iron content of cows' or goats' milk.[3]

Blauberg[4] reports the following percentage absorption of the ash of cows' and human milk:

Kind of Milk	Subject	Per Cent. Milk Ash Absorbed
Cows'	Infant.	60.70
Diluted cows'	"	53.72
Human	"	79.42
Human	"	81.82
Cows'	Adult.	53.20

The quantity of calcium in cows' milk is in excess of the needs of the human infant.

The absorption of the energy-containing constituents of the milk is remarkably constant. This is illustrated in the following table made from Rubner's experiments,[5] which shows the physiologic utilization of the total calories of milk:

	Per Cent. of Calories Absorbed
Human milk	91.6 to 94.0
Diluted cows' milk	90.7
Diluted cows' milk + milk-sugar	92.2
Same given to stunted infant	87.1
Cows' milk given to an adult	89.8

As regards the relative composition of average cows' and human milk five and one-half months after parturition, the following comparison may be made:

PERCENTAGE COMPOSITION OF COWS' AND HUMAN MILK

	Cows'		Human	
	I[6]	II[7]	I[8]	II[9]
Protein	3.41	3.2	1.0	1.52
Fat	3.65	3.9	3.0	3.28
Milk-sugar	4.81	5.1	6.4	6.50

[1] Jolles, A., and Friedjung, J. K.: Arch. exper. Path. u. Pharm., 1901, **46**, 247.
[2] Edelstein, F., and v. Csonka, F. : Biochem. Z., 1911–12, **38**, 14.
[3] Elvehjem, C. A., Herrin, R. C., and Hart, E. B.: J. Biol. Chem., 1926–27, **71**, 255.
[4] Blauberg, M.: Z. f. Biol., 1900, **46**, 44.
[5] Rubner, M., and Heubner, O.: *Ibid.*, 1899, **38**, 380. For further statistics of absorption consult Tangl, F.: Pflüger's Arch. gesam. Physiol., 1904, **104**, 453.
[6] Rubner, M.: Von Leyden's "Handbuch," 1903, **1**, p. 95.
[7] Van Slyke, L. L.: "Modern Methods of Testing Milk and Milk Products," New York, 1907. Average of 5552 American analyses.
[8] Rubner, M., and Heubner, O.: Z. ex. Path. u. Therap., 1905, **1**, 1.
[9] Söldner: Z. f. Biol., 1896, **33**, 66. Average of the milk of 5 women.

Or, expressed in the relative calorific value of the different constituents, this comparison may be given:[1]

PERCENTAGE DISTRIBUTION OF CALORIES IN COWS' AND HUMAN MILK

	Cows' I	Human I
Protein	21.3	7.4
Fat	49.8	43.9
Milk-sugar	28.9	48.7

Here, then, there are tremendous differences of composition, which fact forces the conclusion that cows' milk is not to be substituted for human milk in rearing a child.

Patein and Daval[2] find that human milk after the first month of lactation contains but 0.8 to 1 per cent. of casein.

Another distinction between cows' and human milk is that the former contains but little extractive nitrogen, while the latter may contain 18 to 20 per cent.[3] in that form. These nitrogenous extractives contain a considerable amount of carbon. Meigs and Marsh[4] state that human milk contains 1 per cent. of unknown extractive substances which are almost free from nitrogen. This is probably one of the causes of the increase of the $\frac{C}{N}$ ratio (see p. 38) to over unity in the urine of breast-fed infants.

A recent analysis[5] of the composition of cows' milk shows the following distribution of nitrogen among its constituents:

	Mg. in 100 C.C.		Mg. in 100 C.C.
Total N	446.4	Albumose N	33.1
Protein N	392.0	Peptone N	19.5
		Purin base N	2.3
Rest N	74.4	Uric acid N	1.6
		Creatinin N	1.4
		Creatin N	2.6
		Amino-acid N	2.9
		Urea N	10.1
		Total rest N	73.5

From the standpoint of chemical analysis Abderhalden[6] could find no distinctive quantitative difference between the amounts of various amino-acids in human and bovine milks.

[1] Rubner, M.: "Energiegesetze," 1902, p. 418.
[2] Patein, G., and Daval, L.: Journal de Pharm. et de Chimie, 1905, **22**, 193.
[3] Rubner, M., and Heubner, O.: *Loc. cit.*
[4] Meigs, E. B., and Marsh, H. L.: J. Biol. Chem., 1913–14, **16**, 147.
[5] Bleyer, B., and Kollmann, O.: Biochem. Z., 1924, **153**, 459.
[6] Abderhalden, E., and Langstein, L.: Z. physiol. Chem., 1910, **66**, 8.

An analysis[1] presents the following data as regards the probable composition of human milk:

	Per Cent.
Fat	3.30
Lactose	6.50
Proteins combined with calcium	1.50
Calcium chlorid	0.059
Monopotassium phosphate	0.069
Sodium citrate	0.055
Potassium citrate	0.103
Monomagnesium phosphate	0.027

The large protein content of cows' milk may be bad for the child. In the first place it clots in a heavy mass in the baby's stomach; and in the second place, even though it be digested, it is relatively much above the requirement of the organism, and its specific dynamic action increases the amount of heat produced. (See p. 557.)

If cows' milk be diluted with 2 or more parts of water its protein content may approach that of human milk and its precipitation by rennin in the stomach is in the form of flakes. The writer's father,[2] following a suggestion of Abraham Jacobi, used oatmeal or barley water as a diluent of milk given to babies. The precipitation of cows' casein takes place in very fine flakes when the milk is mixed with barley water, as was shown by Chapin.

Chapin's observations, in which the writer assisted, have been confirmed by White,[3] who says that this action is due to the presence of $\frac{3}{4}$ to 1 per cent. of dissolved starch.

The dilution of cows' milk, however, reduces the quantity of fat and carbohydrates, and these must therefore be added to the milk in order to make a proper diet for a child.

To obtain a sufficient fat content, "top milk," rich in fat, may be taken from milk which has been standing, and may be mixed with water. Milk-sugar may then be added.

Such a milk, called "modified milk," was first introduced by Rotch, of Boston. Infants are brought up on it with greater success than was the case when undiluted cows' milk was given.

THE METABOLISM OF CHILDREN

The Metabolism of the Prematurely Born.—Rubner and Langstein[4] have investigated the metabolism of two prematurely born

[1] Bosworth, A. W.: J. Biol. Chem., 1915, **20**, 707.
[2] Lusk, W. T.: "Science and Art of Midwifery," New York, 1891, p. 258.
[3] White, F. W.: J. Boston Soc. of Med. Sc., 1900, **5**, 130.
[4] Rubner, M., and Langstein, L.: Arch. f. Physiol., 1915, p. 39.

infants. One of them was born at the end of the seventh month of pregnancy and weighed 2050 grams. On the eighth day the child weighed 1900 grams, and then gained an average of 28 grams daily until the twenty-seventh day, when it weighed 2360 grams. At this point respiration experiments were introduced. During the next eleven days the child gained 39 grams daily. During this same period the child received each day 1.04 grams of nitrogen in milk and retained 0.52 gram, or 50 per cent. of the intake. At this period, which would have corresponded to the beginning of the

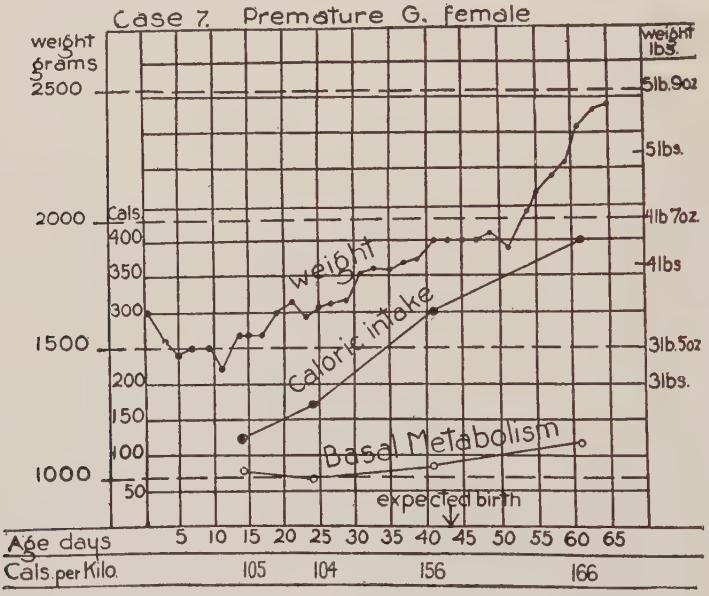


Fig. 30.—Case 7. Food intake, growth and metabolism of a prematurely born female infant. (Talbot.)

eighth month of pregnancy, the addition of protein to the child amounted to only one-half that computed by Hoffström for the fetus of the same age. The fat retained per day averaged 14.6 grams. The diet contained 126 calories per kilogram of body weight, of which 73 were used for heat production (973 calories per square meter per day) and 53 were deposited in the growing infant. In all, 42 per cent. of the calories ingested in the food were retained for growth, a remarkably large amount. The so-called "growth impulse" must have been very great. The second prematurely born infant showed

the same capacity for protein retention as the first, but the amount of fat retained was much less.

The metabolism of the prematurely born infant was carefully investigated by Talbot and his associates,[1] who found a very low metabolism, much lower than in the newborn. There was no gain in weight until the child could ingest 200 calories, and the only food fit to accomplish this was mother's milk. A large amount of the intake was used for the growth of the tissue because relatively there is a greater amount of growth than in normal babies. One of Talbot's instructive charts is here reproduced (Fig. 30).

Marsh and Murlin[2] investigated the metabolism of 21 prematurely born and undersized infants, including 5 pairs of twins. The basal metabolism was 6.48 calories per hour and 26.25 calories per square meter of surface. The metabolism was only 2.04 calories per kilogram. Crying doubled the metabolism.

Talbot's cases showed an average of 24.88 calories per square meter per hour but in the earlier 2 weeks of only 20.6 calories per square meter of body surface.

Marsh and Murlin showed that increasing the amount of food raised the heat production through the specific dynamic action of the increased ingesta:

Food Breast Milk Gm.	Calories Produced per Sq. M.
26	24.2
68	29.4
+42	+5.2 = +21 per cent.

The Metabolism of the Newborn.—Plaut[3] presents an interesting compilation of figures regarding the metabolism of newborn animals per square meter of surface. That basal conditions of complete rest existed in all these experiments is not likely. But that a mouse 9 days old weighing 3.8 gm. should produce 904 calories per square meter of surface and a dog 10 days old 902 calories per square meter, should give pause to those who think such correlations are without significance. That the metabolism of a chick just out of the egg should be out of line with that of the mammals here included does not

[1] Talbot, F. B., Sisson, W. R., Moriarty, M. E., and Dalrymple, A. J.: Am. J. Dis. Child., 1922, **24**, 95.
[2] Marsh, M. E., and Murlin, J. R.: *Ibid.*, 1925, **30**, 310.
[3] Plaut, R.: Z. f. Biol., 1921, **73**, 141.

appear necessarily to obscure the general outline of the picture. Plaut's table is as follows:

RESPIRATION EXPERIMENTS ON NEWBORN ANIMALS

	No. of Animals	Day of Life	Body Wt.	Cals. per Sq. Meter per Day
			Gm.	
Cats I	3	1	117	876
		20	300	950
II	3	1	133	938
		5	167	919
Dogs	2	1	401	750
	1	10	650	902
Guinea-pigs	2	1	65	982
	2	25	145	1039
Rabbits	1	2	40	974
	2	9	75	935
Mice	4	2	1.2	717
	3	9	3.8	904
Chickens*	2	1	40	587
	2	11	52	843

* Results obtained after food and at nest temperature.

Hasselbalch[1] in 1904 investigated the metabolism of newborn babies and established the fact that the respiratory quotient of the child at birth was about unity, which indicates that the earliest source of its energy requirement is derived from stored glycogen. This was confirmed by Bailey and Murlin, who also showed that on account of insufficient nourishment the respiratory quotient fell to the fasting level within twenty-four hours.

Bailey and Murlin[2] published observations upon the metabolism of 6 newborn infants shortly after the publication of a preliminary communication by Benedict and Talbot[3] upon the same subject, which they later reported in detail.[4] In the same year Murlin and Hoobler[5] published their results concerning the energy metabolism of 10 hospital children and at the same time summarized the work of their predecessors and contemporaries. They pointed out that the heat production of sleeping children between the ages of two months and one year was about 2.5 calories per kilogram per

[1] Published in Danish; English translation by F. G. Benedict and F. B. Talbot in "The Physiology of the Newborn Infant," Carnegie Institution of Washington, Bull. 233, 1915.

[2] Bailey, H. C., and Murlin, J. R.: Am. J. Obst., 1915, **71**, 526.

[3] Benedict, F. G., and Talbot, F. B.: Am. J. Dis. Child., 1914, **8**, 1.

[4] Benedict, F. G., and Talbot, F. B.: "The Physiology of the Newborn Infant," Carnegie Institution of Washington, Bull. 233, 1915.

[5] Murlin, J. R., and Hoobler, B. R.: Am. J. Dis. Child., 1915, **9**, 81.

hour; in other words, they state that 60 calories per kilogram per day may be called the heat production of normal, recently fed, sleeping

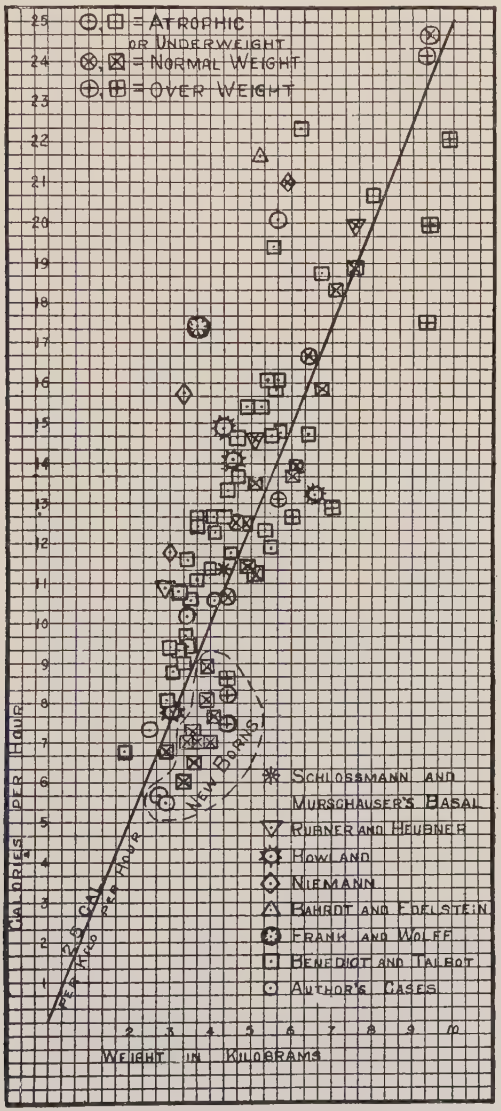


Fig. 31.—Showing relation of heat production to body weight. All infants whose metabolism has been studied by von Pettenkofer or Regnault-Reiset methods (Murlin).

infants. The newborn babes had a metabolism less than this, which did not exceed 48 calories per kilogram per day. Murlin was the

first to emphasize that when age was taken into consideration there was a constancy in the heat production per square meter of surface.

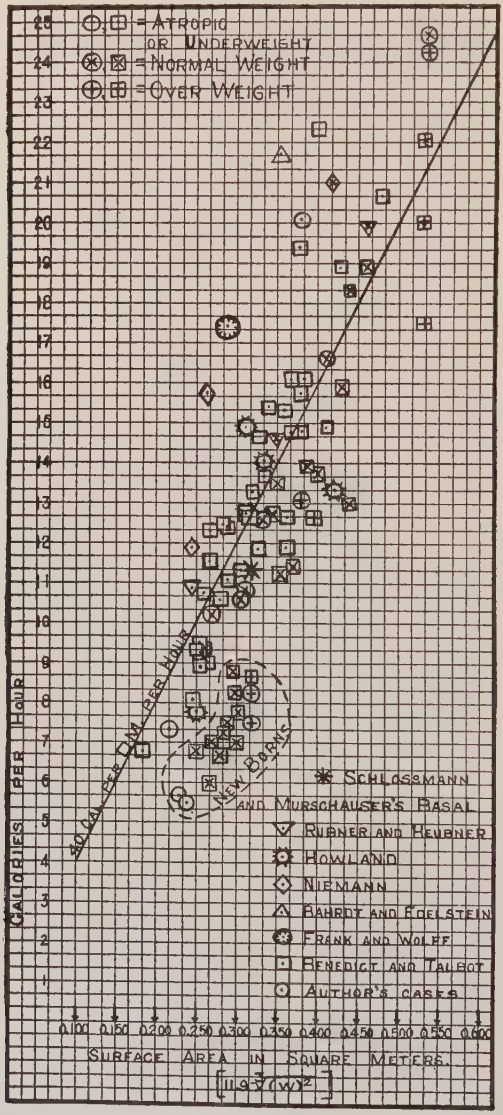


Fig. 32.—Showing relation of heat production to skin surface. All infants whose metabolism has been studied by von Pettenkofer or Regnault-Reiset methods (Murlin).

Two charts taken from Murlin illustrating the relations described are reproduced in Figures 31 and 32, and the chart of Du Bois showing

the influence of age on metabolism should also be consulted. (See p. 138.)

In gratifying accord with this interpretation was the subsequent announcement of Benedict and Talbot that in 48 newborn infants 80 per cent. of their cases showed a metabolism which was within 6 per cent. of 640 calories per square meter per day. Per kilogram of body weight 48 calories is given by them as the minimum metabolism.

Murlin, Conklin, and Marsh[1] have recently repeated this work, making 234 determinations upon 50 new-born infants, aged 6 hours to 14 days. They report that the basal metabolism of 38 of these newborn infants averages:

Per hour	6.67 calories
Per kg. per hour	2.00 "
Per sq. m. surface per hour	29.16 "

Lissauer's formula, $0.103\ \sqrt[3]{\text{Weight}^2}$ kg., was used to determine the surface area. Their determinations show that the maximum heat production occurred during the second 24 hours after birth and then fell steadily until the 6th day, when it began to rise. This is shown in the following table:

Days of age	1	2	3	4	5	6	7	8
No. of observations	8	7	23	7	14	5	9	9
Cals. per hour	6.8	7.2	6.7	6.6	6.0	5.5	6.1	6.3
Cal. per sq. m. surface per hr.	28.0	30.0	29.3	28.6	27.7	26.4	27.4	27.8
Cal. per kg. per hr.	1.88	1.99	2.01	1.96	1.97	1.89	1.98	1.90

It should be added that Talbot,[2] in his excellent review of the basal metabolism of children, says that no justification of this conclusion is to be found in the Benedict and Talbot series of newborns. In Murlin's work there was no correlation between the heat production and the pulse rate. Computations of heat production based on surface area measurements were as usual more accurate than those based on body weight.

Crying 1 per cent. of the time raised the basal metabolism 1 per cent., that is, doubled it. If, instead of giving a small amount of milk before the experiment, a large amount of milk was given, the metabolism increased 7 to 10 per cent.

In practical dietetics one must add to the maintenance requirement sufficient nourishment to provide for the crying of the

[1] Murlin, J. R., Conklin, R. E., Marsh, M. E.: Am. J. Dis. Child, 1925, **29**, 1.
[2] Talbot, F. B.: Physiol. Rev., 1925, **5**, 492.

child, and also the very considerable quota to meet the demands of growth.

The amount of energy expended by the crying of an infant will vary with the infant, for during this form of exercise the heat production is raised at least 40 per cent. It is certain that Heubner's figure of 100 calories per kilogram of body weight during the first month of the infant's nutrition is in excess of the requirement. Probably 80 calories per kilogram of body weight will be found to suffice during the whole of the first year of life, and the physician should remember very definitely the lower limits. It is not infrequent that a crying infant is merely hungry.

The Metabolism of the Growing Child.—The early experiments of Rubner led him to conclude that, although the metabolism of an infant weighing 4 kg. was the equivalent of 422 calories a day and of an adult weighing 40 kg., 2106 calories, yet per square meter of surface the metabolism was the same.

Rubner and Heubner[1] made a historic contribution to this subject, but as the child cried and struggled while in the respiration apparatus, the results are not comparable with those obtained under modern conditions. The child, which weighed 10 kg., produced 660.5 calories per day after ingesting 634.5 calories in the diet. According to Benedict and Talbot's tables, the basal metabolism of a child weighing 10 kg. is 545 calories. The heat production of 660 indicates that 115 extra calories might have been expended in crying. If Murlin's computation is correct, the baby cried 20 per cent. of the time. The milk given this infant contained protein to the extent of 7 per cent. of its calories, of which 2 per cent. was added to the body and 5 per cent. was metabolized. The metabolism of an infant could therefore be maintained on a diet in which 5 per cent. of the energy was supplied by protein and 95 per cent. by carbohydrate and fat. The administration of tea to the infant instead of food left the metabolism unchanged This led the investigators to conclude that food exerted little specific dynamic action in the nursling. A crying baby is not a fit subject for such a study. The fact, however, was established later by Howland, as we shall see.

Schlossmann and Murschhauser[2] note that, whereas during the first and second days of fasting an infant may eliminate 16 and 15

[1] Rubner, M., and Heubner, O.: Z. exper. Path. u. Therap., 1905, **1**, 1.
[2] Schlossmann, A., and Murschhauser, H.: Biochem. Z., 1913, **56**, 355.

milligrams of urinary nitrogen per kilogram of body weight, return to a normal diet results in the elimination of only 8 milligrams per kilogram. This illustrates the avidity with which, under favorable conditions, all available protein is used for growth. This would eliminate the specific dynamic action of ingested protein (see p. 297).

W. Camerer, Jr.,[1] showed that a breast-fed infant nine months old may ingest 480 calories in the milk, produce 420 calories in metabolism, and add 60 calories to his body, or 15 per cent. of the energy content of the diet. In this case 40 per cent. of the protein intake was added to the growing organism.

Rubner and Heubner[2] have reported a respiration experiment on a child seven and a half months old nourished with modified cows' milk. The intake was 682.8 calories, the metabolism 593.2, leaving 89.6 calories, or 12.2 per cent. for addition to the child's organism.

It is remarkable that a child's intuitive appetite should determine the ingestion of nutriment necessary to cover the energy requirement of his organism, and a small addition for normal development. A reduction of 15 per cent. in the intake of food would bring his prosperous growth to a standstill.

Heubner[3] says that the average normal infant requires 100 calories per diem per kilogram of body weight for normal nutrition during the first three months of his life, 90 calories during the second three months, and 80 and less thereafter. The energy content of the food should never sink below 70 calories per kilogram, which is about the maintenance minimum.

The so-called "scientific feeding" of infants is unworthy of the name unless the calorific requirement is carefully considered. From lack of this knowledge babies are frequently systematically starved. The writer of this book once knew a physician to give an infant oatmeal water and lactose as a steady diet and to wonder why the infant cried all night! Appreciation of the vitamins is of course essential, but the energy for maintenance, activity and growth is dependent on protein, fat and carbohydrate, not on vitamins expressed in fractions of a milligram.

It is evident from this discussion that the fundamental, basal metabolism of the infant cannot be determined during long periods

[1] Camerer, W., Jr.: Z. f. Biol., 1902, **43**, 1.
[2] Rubner, M., and Heubner, O.: *Ibid.*, 1899, **38**, 345.
[3] Heubner, O.: Berliner klin. Wchnschr., 1901, **38**, 449.

in which crying is an ever-entering factor. Schlossmann and Murschhauser,[1] for example, have found that the metabolism of an infant may double during an hour of movement when the baby would not be quieted, but cried intensely. The resting metabolism of this child five months old was estimated at 859 calories per square meter of surface in twenty-four hours. The same authors[2] have shown that a change of environmental temperature between 22° and 17° C. has no influence upon the heat production of the infant.

The work upon the subject of the metabolism of children was begun in the United States by John Howland.

Howland's[3] experiments are the only reported calorimetric observations upon infants, and the close concordance between direct and indirect calorimetry as observed in hourly periods in these experiments gave confidence to subsequent observers that by the careful determination of the respiratory metabolism alone the actual heat production could be readily computed.

Howland gives the following summary of work with a normal male infant (Child I) five months old and with a boy (Child III) six months old who weighed only 3 kilograms and was literally "skin and bones." The children were fed with diluted milk with the addition of milk-sugar:

CORRESPONDENCE BETWEEN DIRECT AND INDIRECT CALORIMETRY IN INFANTS

	Food	Calories per Sq. M. per Day		Difference in Per Cent.
		Direct	Indirect	
Child I	Milk	1046	1084	
		1113	1174	2
		1196	1164	
	Same + nutrose	1218	1179	3
	Same + nutrose	1204	1180	
		1235	1212	0.6
		1181	1250	
	Fasting (asleep)	1106	1177	
	(awake	1226	1156	2
	(crying)	1301	1243	
Child III	Milk	858	793	
		913	933	2
	Milk	825	840	

[1] Schlossmann, A., and Murschhauser, H.: Biochem. Z., 1910, **26**, 14.
[2] Schlossmann, A., and Murschhauser, H.: *Ibid.*, 1911, **37**, 1.
[3] Howland, J.: Z. physiol. Chem., 1911, **74**, 1; Trans. XV International Congress on Hygiene, 1912, **2**, Part 2, 438.

To compute the surface area of children Lissauer's formula ($0.103 \sqrt[3]{\text{Weight in kg.}^2}$) is usually employed, though Howland has suggested one of still greater accuracy.

Just as in the case of the adult (see p. 172), the emaciated organism of an infant produces less heat per square meter of surface than the normal organism. Howland reported another case in which he determined the heat production of an eight-year old child, emaciated to a most extreme degree and almost devoid of musculature. The average heat production was 13.2 calories per hour, or 809 per square meter of surface per day.

Lusk[1] pointed out that, whereas the metabolism of the dog and of a human dwarf was about 775 calories per square meter per day under conditions of complete rest, that of the two normal infants who were the subjects of Howland's experiments was 1100 calories per unit of surface. Howland's work furthermore showed that when nutrose was added to the diet there was a pronounced specific dynamic action, the heat production rising from 14.9 to 18.8 calories per hour, an increase of 26 per cent. Vigorous crying also increased the metabolism in the same child from 14.85 to 20.6 calories per hour, an increase of 39 per cent. (See p. 553.)

Howland gave no food to one of the children during a night period of 18 hours and then gave weak tea with a little saccharin, after which the baby slept quietly. The heat production was not greater than when the infant received its usual nourishment. The respiratory quotient was 0.85, indicating that the glycogen store had not been depleted. It seems probable that the factors involved in the growth impulse leading to the deposit of extra food metabolites for the purpose of growth may tend to reduce that plethora of metabolites which leads to the specific dynamic action, so that when the small and frequent meals of the nursling are taken only little specific dynamic action appears. The case is different when protein in excess is given, as after the ingestion of Finkelstein's "Eiweissmilch," which has a profound specific dynamic action which these experiments of Howland for the first time demonstrated.

These investigations were performed in the winter of 1910–11, and it was only on account of the demands upon the calorimeter for other investigations that Murlin was prevented from immediately continuing them. During the time when Murlin was building his own

[1] Lusk, G.: Trans. XV International Congress on Hygiene, 1912, **2**, Part 2, 400.

respiration apparatus for infants Benedict and Talbot also entered the field. The result of this is that we now have a wealth of data, which is gratifying in every way except that there is a deadlock upon the subject of a common standard.

STANDARDS OF BASAL METABOLISM IN CHILDREN

In 1914 Benedict and Talbot[1] published a monograph which included metabolism studies upon 37 infants, as the result of which they concluded, "We find ourselves thoroughly convinced that the metabolism is determined not by the body surface, but by the active mass of protoplasmic tissue."

In the otherwise commendable monograph of Talbot to which reference has been made charts showing the calories produced per square meter of surface with regard to age are not included. However, this monograph gives:

a. surface area of boys and girls of different weights;

b. total basal calories of boys and girls of different weights.

If we employ Talbot's values for these factors and interpolate the probable ages for the weights, we obtain the following results:

Approximate Age	Weight	Calories per Sq. M. Surface			
		Boys		Girls	
		Per Day	Per Hr.	Per Day	Per Hr.
Yrs.	Kg.				
1–2	10	1108	46.2	1097	45.7
6	20	1039	43.3	1011	42.2
10	30	1005	41.9	975	40.6
12	38	981	40.9		

The metabolism of boys appears to be slightly higher than that of girls if the measurements be made on this basis. However, in another article, Talbot[2] gives these curves, which are here reproduced and which show a decided differentiation between the metabolism of the boys and girls. These charts of Talbot are based on 10 years of painstaking care and are of the greatest value. (Figs. 33, 34, and 35.)

Du Bois[3] found that the basal metabolism of 7 boys reached 49.9 calories per square meter of surface per hour when they were 12 to

[1] Benedict, F. G., and Talbot, F. B.: "The Gaseous Metabolism of Infants," Carnegie Institution of Washington, Bull. 201, 1914.

[2] Talbot, F. B.: Am. J. Dis. Child., 1921, **21**, 519.

[3] Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 887.

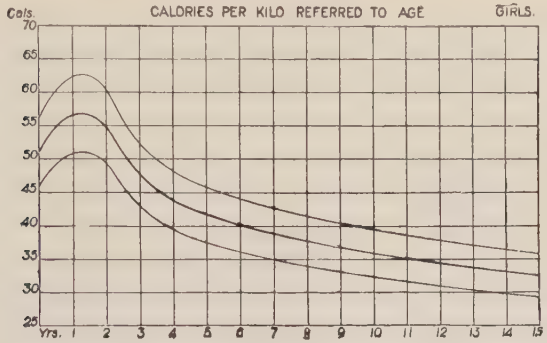


Fig. 33.—Basal metabolism, calories per kilogram of body weight for 24 hours of girls at different ages. The curve is projected from 12 years upward (Talbot).

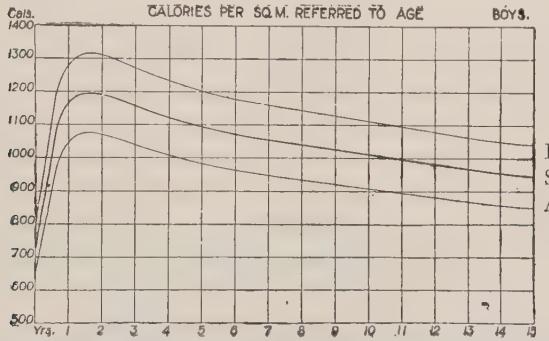


Fig. 34.—Basal metabolism, calories per square meter of body surface for 24 hours of boys at different ages. The curve is projected from 12 years upward (Talbot).

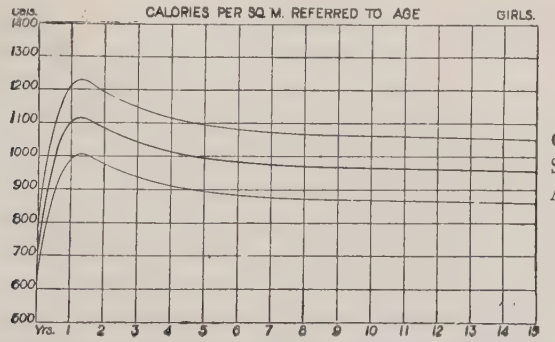


Fig. 35. Basal metabolism, calories per square meter of body surface for 24 hours of girls at different ages. The curve is projected from 12 years upward (Talbot).

(Figs. 33, 34 and 35, reproduced by permission from E. F. Du Bois' "Basal Metabolism in Health and Disease," Lea & Febiger, Philadelphia, 2d ed., 1927, p. 141.)

13 years of age, and 2 years later when the basal metabolism of the same boys was investigated by Olmstead, Barr, and Du Bois[1] it was found that it had fallen to 44.1 calories, or 13 per cent. less than it had been 2 years previously. It was still 11 per cent. higher than the basal metabolism of an adult man. In the 3 youngest boys, during their 12th year the basal metabolism represented a higher level in actual calories produced than in the 14th year, although the boys had gained 35 to 50 per cent. in weight. The conclusion was drawn that there was a rise in basal metabolism of boys just before the onset of puberty. The values are admittedly too high. Du Bois[2] finds in the work of Bedale[3] and of Mac Leod[4] ground for believing that a similar rise in metabolism occurs in girls just before puberty.

On the other hand, Benedict and Talbot and also Sandiford and Harrington[5] are agreed that the decrease in calories progresses very regularly and appears to be nearly if not absolutely a straight line function for both boys and girls. The latter group of workers obtained values from 157 normal school children between the ages of 5 and 17 years and state that the true mean of basal metabolism lies between the values of Du Bois and of Benedict and Talbot.

A fine analysis of the *basal metabolism of girls* has been made by Blunt[6] and her associates, who determined the basal metabolism on or near the birthday of 46 girls. She has compared her own results with those of MacLeod, and presents the following table:

BASAL METABOLISM OF GIRLS BETWEEN ELEVEN AND SIXTEEN YEARS OF AGE

Age	Number of Subjects		Calories					
			Per 24 Hrs.		Per Kg. per 24 Hrs.		Per Sq. M. per Hr.	
	Mac Leod	Blunt *et al.*	Mac Leod	Blunt *et al.*	Mac Leod	Blunt *et al.*	Mac Leod	Blunt *et al.*
11	4	13	1191	1188	29.2	33.7	37.5	41.4
12	18	18	1295	1309	32.3	32.4	41.3	42.4
13	22	15	1365	1437	31.1	30.2	41.0	41.0
14	13	3	1308	1380	26.7	31.1	36.6	40.8
16	..	2	....	1317	....	25.1	....	34.5

[1] Olmstead, W. H., Barr, D. P., and Du Bois, E. F.: Arch. Int. Med., 1918, **21**, 621.
[2] Du Bois, E. F.: "Basal Metabolism in Health and Disease," Philadelphia, 2d ed., 1927, p. 147.
[3] Bedale, E. M.: Proc. Roy. Soc. (London), 1923, B, **94**, 368.
[4] MacLeod, G.: Inaug. Diss., Columbia University, 1924.
[5] Sandiford, I., and Harrington, E. R.: J. Biol. Chem., 1925, **63**, p. xxxv.
[6] Blunt, K., Tilt, J., McLaughlin, L., and Gunn, K. B.: *Ibid.*, 1926, **67**, 491.

The work of Bedale is in accord with this except that the 11 to 12 year groups are higher. Bedale found that sex had no influence upon the basal metabolism of younger children. Following puberty it is evident that in both sexes there is a decline in the metabolism until the basal level of maturity is reached. At the age of 14 to 16 the metabolism of boys is 7 per cent. higher than that of girls according to Du Bois.

Blunt's series of cases of 11 girls who were 13 per cent. under weight showed a metabolism which was −3.9 per cent. less than the average value per square meter. In still another group 13 girls who were 18 per cent. over weight showed an entirely normal metabolism. Still another group of 9 decidedly emaciated girls (−19 per cent. under weight) had a basal metabolism of +6.6 per cent. above the normal average. The authors suggest that perhaps their metabolism was as high as if their surface had been increased by fat. This has been confirmed by Wang and his associates[1] who say that undernourished, pale, and sickly children belonging to excitable foreign parents showed basal metabolisms which they would have had if they had been up to normal weight.

It seems unnecessary to develop the details further, especially in view of the critical summaries of Talbot and more recently of Du Bois in the second edition of his book.

THEORETICAL

Above have been collected various data which may be assembled as follows:

	Metabolism in Calories per Sq. Meter per Hr.
Premature infants	26.3
Newborn infants	29.2
Boys: 1 year old	46.2
6 years "	43.3
10 " "	41.9
12 " "	40.9
Girls: 11 " "	41.4
12 " "	42.4
13 " "	41.0
14 " "	40.8
16 " "	34.5

These values are not given to establish anything more than the general trend of metabolic activity in different ages.

[1] Wang, C. C., Kern, R., Frank, M., and Dunwiddie, J.: J. Biol. Chem., 1925, **63**, p. lxi; Am. J. Dis. Child., 1926, **32**, 350.

Now what is the cause of the variations which occur with age?

1. Murlin long ago called attention to the fact that the human infant has a highly undeveloped nervous system, and that coördination between heat production and heat loss is not adequately developed at birth.

2. Rubner[1] gives the following comparison between the composition of an adult man and a newborn baby:

	Man Per Cent.	Newborn Per Cent.
Skeleton	15.0	15.7
Muscles	41.8	23.5
Fatty tissue	18.2	13.5
Glands, and balance	24.1	47.3

Moulton[2] recounts the statement of Voit that with increased age and development there is an increase in fat content and the displacement of water by fat. Moulton shows that accompanying the displacement of water there is also a large deposit of muscle protein. Water decreases in percentage until "chemical maturity" is established. Allowing from the time of conception, animals reach chemical maturity after about 4.5 per cent. of their lives, in cattle after 435 days, in guinea-pigs after 114 days. Animals vary in composition at birth; the less the maturity the greater is the quantity of water. Thus mice and rats contain 87 per cent. of water at birth, while cattle and guinea-pigs contain only 77 per cent.

Reference to the table on p. 550 will show that the newborn mouse had a metabolism of 717 calories and the newborn guinea-pig one of 982 calories per square meter of surface per day.

The constant nitrogen retention under the influence of the growth impulse is strikingly shown in two boys reported by Ruotsalainen.[3] The boys, who were 9 and 10 years old, when taking a mixed diet containing 10 to 11 gm. nitrogen daily, added about 1 gm. each to their body substance. On raising the protein nitrogen in the diet to 24 gm. the daily nitrogen retentions on the first day were +6.8 and +8.6 gm. nitrogen, but 10 days later when the reservoirs for "deposit protein" were filled, the retentions, even during this high protein diet, fell to +1.1 and +1.5 gm. nitrogen.

3. It has definitely been established that young tissue has an inherently higher metabolism that adult tissue (see p. 525).

[1] Thom's "Handbuch der Pharmacie," Berlin, 1924, **3,** p. 4.
[2] Moulton, C. R.: J. Biol. Chem., 1923, **57,** 79.
[3] Ruotsalainen, A.: Skan. Arch. Physiol., 1921, **41,** 33.

These are the factors which may have a potent influence.

Talbot, in his article in *Physiological Reviews*, gives an enlightening contrast between the metabolism of three infants of the same age and height but of different weights.

THE INFLUENCE OF WEIGHT ON THE METABOLISM OF INFANTS OF THE SAME AGE, SEX, AND HEIGHT

Benedict and Talbot Number	Age	Weight	Height	Body Surface Du Bois	Calories per 24 Hrs.		
					Total	Per Kg.	Per Sq. M.
	Mos.	Kg.	Cm.	Sq. M.			
129	3	7.1	62.0	0.380	311	44	828
130	3	6.0	63.0 (?)	0.341	305	51	888
133	$3\frac{1}{2}$	5.8	62.5	0.327	329	57	1006

As regards these young infants, the fatter the child the lower the metabolism per square meter of surface. It is possible, however, that the somewhat greater maturity of the protoplasm had something to do with the higher metabolism of Infant 133. We have also learned two things: one, that obesity itself will not necessarily lower metabolism in later life; and two, that sometimes undernutrition, when accompanied by food, brings about a rise in the metabolism to the level which ought normally to be attained by an individual of a given height. All the experiments on children must perforce be made after they have taken their milk and gone to sleep. If Infant 133 had greedily taken much food its metabolism would have been increased.

This experiment, therefore, does not invalidate the proposition that for *normal* children, from birth onward the metabolism closely follows the law of surface area, varying only with age and, after puberty, with sex. It rises rapidly during the first year of life at a time when new youthful protoplasm is being added to the body and then declines slowly until maturity in the 18th or 20th year of life.

It would be a valuable and important experiment to test this youthful protoplasm at the time when a boy becomes strong enough to ride a stationary bicycle and to see whether the mechanical efficiency of the muscles is the same as in the adult. But care must be exercised not to overstrain the boy.

Wilson, Levine, Rivkin, and Berliner[1] state that the respiratory quotient of a child taking exercise is unchanged from that of the basal value. Examples are as follows:

	Metabolism	R. Q.
Rest	Basal	0.788
Active	+40 per cent.	0.793
Rest (no food for 37 hrs.)	Basal	0.777
Active (no food for 42 hrs.)	+28 per cent.	0.781

Levine and Wilson[2] have established for children, as Du Bois and Soderstrom did for adults (see p. 145), that 24 per cent. of the calories of the basal metabolism are lost through the evaporation of water.

THE RELATION OF GROWTH TO THE INTAKE OF CALORIES

Oppenheimer[3] first called attention to the fact that the growth in grams of normal breast-fed children of the same age may be nearly proportional to the quantity of milk ingested. Here the milk presumably had the same calorific value throughout the experiment, although this could not be determined. The quantity of milk taken at each meal was found by weighing the infant before and after nursing. Oppenheimer's table is here reproduced:

GROWTH IN GRAMS FOR 1 KG. MILK

Month	Feer's Subject	Oppenheimer's Subject
I	33.8	95.0
II	191.2	201.1
III	120.3	138.5
IV	102.6	103.3
V	57.7	120.8

The proportion of growth to milk given was practically the same during the second, third, and fourth months of these children's lives.

That the growth of suckling pigs may be proportional to the calorific value of the milk has been shown by work accomplished by Dr. L. C. Sanford and Dr. Margaret B. Wilson[4] in the writer's laboratory. Newborn pigs of two litters were reared on skimmed cows' milk and on the same milk fortified with 2 and 3 per cent. of glucose or of milk-sugar. The experiments were continued from fourteen to sixteen days. The results obtained in these experiments are thus tabulated:

[1] Wilson, J. R., Levine, S. Z., Rivkin, H., and Berliner, F.: Am. J. Dis. Child., 1927, **33**, 618.
[2] Levine, S. Z., and Wilson, J. R.: *Ibid.*, p. 204.
[3] Oppenheimer, K.: Z. f. Biol., 1901, **42**, 147.
[4] Wilson, M. B.: Am. J. Physiol., 1902–03, **8**, 197.

GROWTH OF SUCKLING PIGS

	Wilson			Sanford and Lusk		
	Skimmed Milk	Lactose	Glucose	Skimmed Milk	Lactose	Glucose
Weight in grams when born	1,322	1,295	1,485	1,000	1,050	1,152
Weight in grams when killed	2,205	2,435	2,471	1,246	1,890	2,000
Growth in grams	883	1,140	986	264	838	848
Growth in per cent	66.8	88.0	66.4	26.4	79.7	73.6
Milk fed in c.c.	10,925	11,005	9,707	6,826	8,836	9,481
Available calories fed	4,053	5,216	4,620	2,339	3,736	3,972
Growth in grams per liter of milk	81	114	101	38	95	89
Growth in grams per 1000 calories fed	218	215	213	114	222	213

It is seen that the growth of the pigs in grams was directly proportional to the calorific value of the food to the organism. The one exception was that of an ill-nourished pig fed with skimmed milk. This was an improperly nourished animal taking too little food and remaining behind his fellows in normal development. But that 5 out of 6 pigs of different litters, of different sizes and differently fed, should have gained in weight respectively 213, 214, 215, 218, and 222 grams per thousand calories in the food ingested seems more than a coincidence.

It may be further calculated that to form 1 kilogram of body substance containing 28.7 grams of nitrogen and 866 calories requires the ingestion of 4637 calories in the food.

A pig doubles in weight in eighteen days after birth. The pig of Dr. Wilson, brought up on skimmed milk with 3 per cent. of milk-sugar added, nearly doubled in weight in sixteen days.

Comparing the fuel value of sows' milk and that of the skimmed cows' milk to which milk-sugar had been added, the following results are significant. Of 100 calories in the food there are:

	Sows' Milk[1]	Skimmed Milk + 3 Per Cent. Milk-sugar
Protein	19.5	36.5
Fats	72.0	2.5
Carbohydrates	8.5	61.0

It is apparent from this that normal growth of the young organism may be attained by the replacement of fat by milk-sugar in isody-

[1] Calculated from Ostertag, R., and Zuntz, N.: Landw. Jahrb., 1908, **37**, 211.

namic quantity. This fact may become of importance in infant feeding.

Dr. Wilson found, when the pigs reared on these diets were killed and their composition compared with that of 3 pigs of the same litter which were killed at birth, that there was a retention for growth of 18 to 19 per cent. of the energy in the food.

In children Camerer found 15 per cent., Rubner and Heubner 12.2 per cent. so retained.

The percentage of calcium (CaO) in the dry solids of the pigs reared on the various skimmed milks was 8.29, 8.02, and 8.13, showing that the absorption of calcium depended on the growth of the organism, and not on a variation in the quantity ingested.

There is apparently a fixed and definite tendency toward uniform growth. Schapiro[1] found that if young kittens were chloroformed twice daily their growth was retarded in comparison with normal control animals. However, on stoppage of the chloroform treatment, the greater rapidity of growth during an after period fully compensated for the earlier delay in development. (See Chapter XIX, p. 518.)

Lusk has shown that if an amino-acid, such as alanin, be added to the diet of a dog there is a considerable stimulation of metabolism. (See p. 288.) Mendel, in unpublished experiments (cited here by permission), has demonstrated that the addition of alanin to the diet of growing rats has no influence whatever upon their rate of growth. Rubner[2] set forth that the conditions which determine the wear and tear quota of protein metabolism and those which determine growth by the addition of a "growth quota" from protein in the diet, are entirely dissimilar, although without metabolism growth is impossible. Mendel's experiments show conclusively that the stimulation of the general metabolism itself in no way affects the fundamental capacity to grow.

Another instance which demonstrates that the young organism may grow in proportion to the energy ingested in the food is brought to light by calculations based on the work of E. Rost.[3] This author gave meat, fat, and bone-ash to three dogs of the same litter, the experiment starting on the ninety-eighth day of their lives and

[1] Schapiro, A.: Proc. Physiol. Soc., J. Physiol., 1905–06, **33**, p. xxxi.
[2] Rubner, M.: Arch. f. Hyg., 1908, **66**, 43.
[3] Rost, E.: Arbeit. a. d. kais. Gesundheitsamte, 1901, **18**, 206.

continuing eighty-eight days. The writer has thus calculated the results:

	Dog I	Dog II	Dog III
Weight in grams at start	3,200	2,200	4,150
Weight in grams at end	6,280	4,640	8,750
Growth in grams	3,080	2,440	4,600
Growth in per cent	96	110	110
Available calories ingested	24,420	17,336	34,276
Gain in grams per 100 calories ingested	122	141	134

It is worthy of note that these growing dogs, fed with meat and fat, gained in weight nearly the same number of grams per 1000 calories ingested in the food. This law of growth seems reasonably established. It simply expresses the fact that during the normal development of the young of the same age and species a definite percentage of the food is retained for growth irrespective of the size of the individual.

Rubner,[1] in apparent ignorance of this work of Dr. Wilson, has arrived at essentially the same conclusions, and he finds that the law is true regarding all species (horse, calf, sheep, pig, dog, cat, rabbit) except man. He formulates the "law of constant energy expenditure" as follows: *The amount of energy (calories) which is necessary to double the weight of the newborn of all species (except man) is the same per kilogram no matter whether the animal grows quickly or slowly.* To construct one kilogram of normal body substance containing 30 grams of nitrogen and 1722 calories, 4808 calories are required except in the case of man, when six times that amount is needed. This is almost in exact agreement with the experiments of Wilson.

The same principles apply to the growth of rats, as may be seen from the following, calculated from the results of Funk and Macallum,[2] who fed these animals during twenty-eight days:

	Normal Controls		Stunted 20 Days
Number of rats	2	2	2
Weight in grams at start	29	27.5	27.0
Growth in grams	40	42	65
Available calories ingested	1223	1216	1895
Gain in grams per 1000 calories ingested	32.7	34.5	34.3
Calories for construction of 1 gram new tissue	30.6	29.0	29.1

In the work of Hopkins[3] different sets of rats received the same food in different quantities, and the following table has

[1] Rubner, M.: "Das Problem der Lebensdauer und seine Beziehungen zu Wachstum und Ernährung," Munich and Berlin, 1908.

[2] Funk, C., and Macallum, A. Bruce: J. Biol. Chem., 1915, **23**, 413.

[3] Hopkins, F. G.: J. Physiol., 1912, **44**, 425.

been calculated from the results obtained after nine days of food ingestion:

Number of rats used	12	14	18	15
Calories ingested daily per 100 grams of rats, live weight	45	50	55	60
Average initial weights, grams	45.3	45.2	42.2	43.2
Gain in grams of rats	8.8	10.3	11.1	12.8
Gain in grams per 1000 calories ingested	48	51	53	55

Another lot of rats when receiving 65 calories per hundred grams live weight refused to eat all their food. It is of great interest that, notwithstanding the restriction of the dietary below the limits set by the appetite in some of the experiments, yet the gain in the weight of

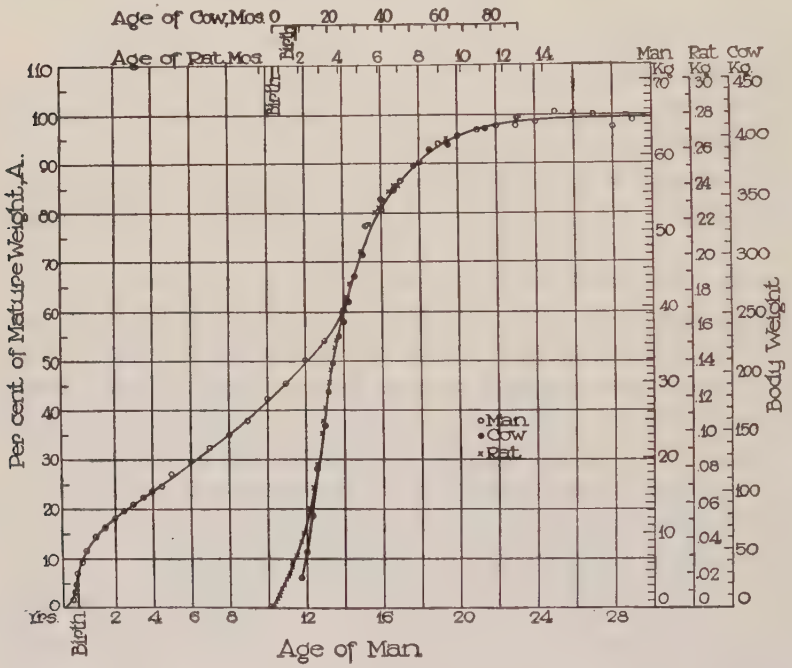


Fig. 36.—Age of man—The growth curves of man, dairy cow, and white rat have the same shape during the phase of growth following puberty (inflection in the curve). Preceding the inflection, however, the curve of man differs from the curve of animals by the extraordinary length of its juvenile period (Brody).

the rats is nearly proportional to the calories in the dietary. Evidently, ample protein, together with calcium and other salts, was present for the construction of new tissue in all the rats. Aron[1] has

[1] Aron, H.: Biochem. Z., 1910–11, **30**, 207.

shown that when growing dogs receive too little energy in their food, the skeleton may grow and the weight increase, though the caloric content of the animal may diminish.

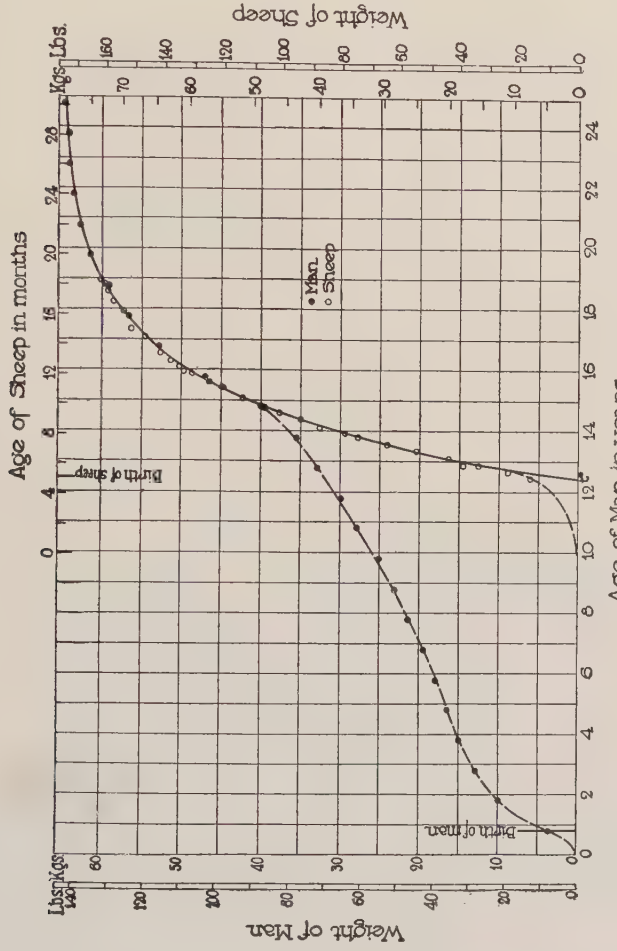


Fig. 37.—Age of man in years—Man and sheep have the same mature weight, but they differ enormously with respect to the time required to reach the mature weight. The difference is particularly striking with respect to the time required to reach puberty (Brody).

Rubner finds in all species the constant retention of approximately the same percentage of the energy ingested, which averages 34.3 per cent., except in the case of man, in whom the energy retained for growth is only 5.2 per cent. He states that 40 per cent. of the energy ingested may be retained for the growth of pigs, whereas Dr. Wilson found only 20 per cent. so retained. This is because the pigs in the

latter case were given skimmed milk, and the added tissue substance was found on analysis to have a heat value of only 866 calories per kilogram, instead of 1722 as assumed by Rubner.

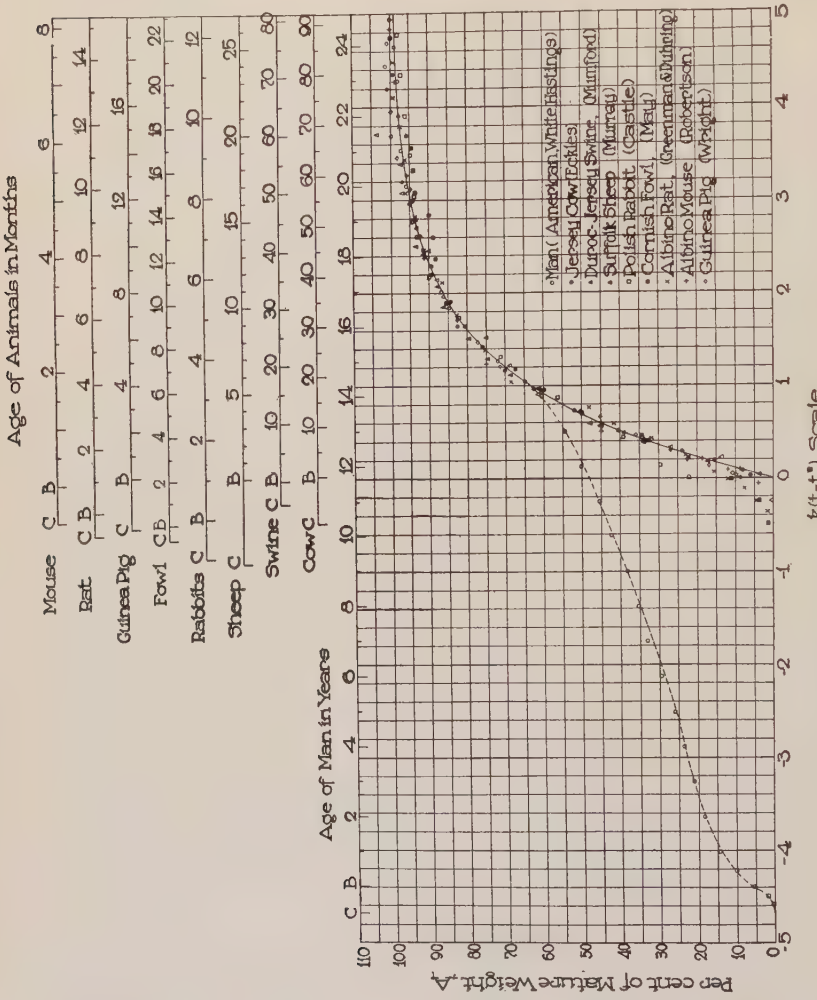


FIG. 38.—Age of animals in months—The growth curves of all domestic animals have the same shape, and there are no gradations between man and animals. It is extremely desirable to determine the position of growth curves of primates other than man with respect to man on one hand and other animals on the other. The upper axes represent ages in absolute units (months for animals and years for man). *C* represents conception and *B*, birth. The numerals on the lower axis represent relative units (Brody).

It is therefore evident that while it requires the same energy equivalent to construct one kilogram of new substance in young animals, the percentage of energy retained for growth may depend upon the amount of fat or starch convertible into fat, present in the diet.

Rubner states that if the requirement for energy in the various animals be placed at 100, then the amount of energy in the food actually ingested by them averages 202. This corresponds to Dr. Wilson's computation of the energy ingested by the growing pigs, which averaged 2100 calories per square meter of surface, as compared with a normal *requirement* of 1089. Dr. Wilson explained this high energy requirement as being partly due to growth and partly

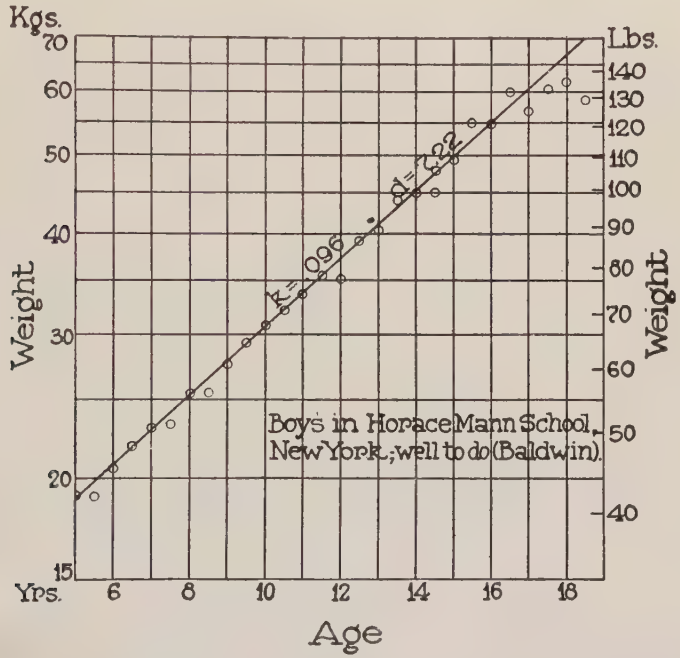


Fig. 39.—Age—During the juvenile period (5 to 13 years), the growth of man in weight takes place at a constant percentage-rate as indicated by the fact that when the logarithms of weights are plotted against the corresponding ages (or what is the same, when the weights are plotted on arithlog paper), the data points are distributed about a straight line. During this period the body weight is doubled once in about 7 years. The percentage-rate (100 k.) of growth is about 10 per year (Brody).

to the extreme activity of the little animals. A human infant does not require this large excess of energy in his food, probably because he is kept warm and sleeps much of the time.

Finally, Rubner has calculated that the quantity of energy metabolized in a kilogram of living cells from maturity to death is the same in different animals, except in the case of man, who again occupies an exceptional position.

This is represented in the following table:

	Body Weight in Kg.	Length of Life in Years after Maturity	Calories Produced per Kg. Adult Body Substance
Man	60	60	775,770
Horse	450	30	169,900
Cow	450	26	141,090
Dog	22	9	163,900
Cat	3	8	223,800
Guinea-pig	0.6	6	265,500

Rubner finds that among the animals each kilogram of adult body substance metabolizes an average of 191,600 calories and then dies. Man alone has power in his protoplasm to use a much larger share of energy in the furtherance of his activities.

The biological distinction of the protoplasm of the growing human being, which separates it from that of the lower mammals, is beautifully exemplified in the growth curves of Samuel Brody,[1] which he has kindly put at my disposal for publication in this book. Following puberty the curve of growth is the same for all the animals, but preceding puberty the growth curve of man shows an extraordinary length of the juvenile period. The legends under the curves are Brody's.

Porter[2] has shown a seasonal variation in the growth of Boston school children, as follows:

Age	Date	Weight	Gain
Months		Kg.	Kg.
106	June, 1914	25.06	
112	Dec., 1914	27.20	+2.14
118	June, 1915	27.92	+0.72

Sunshine in the air and the green things in the food of the summer months are great gifts!

Bunge[3] has recalled the relationship between rapidity of growth and longevity, as originally suggested by Flourens[4] in 1856. This writer believed that if the time of reaching the end of growth be multiplied by 5, the average term of life might be computed. This relationship may be tabulated as follows:

[1] Brody, S., Sparrow, C. D., and Kibler, H. H.: J. Gen. Physiol., 1925–26, **9,** 285.
[2] Porter, W. T.: Am. J. Physiol., 1920, **52,** 121.
[3] Bunge, G.: Pflüger's Arch. gesam. Physiol., 1903, **95,** 606.
[4] Flourens, P., "De la longévité humaine" Paris, 1856, p. 86.

TABLE SHOWING FLOURENS' LAW OF LONGEVITY

	Time in Days from Birth to Double Birth-weight	Time in Years until Full Growth	Deduced Average Longevity in Years	Maximum Recorded Longevity in Years
Man	180	20	90–100	152–169
Camel	...	8	40	100
Horse	60	5	25	50
Cow	47	4	15–20	..
Lion	..	4	30	60
Cat	$9\frac{1}{2}$	$1\frac{1}{2}$	9–10	20
Dog	9	2	10–12	24

Bunge calls attention to the fact that a horse more often lives to be forty than a man to be a hundred. Either the law is false, or man is a too early victim of an improper heredity or environment.

THE MINERAL METABOLISM

As to the subject of the mineral metabolism of growing children, the following work of Jundel[1] is of especial interest. Two boys, K. and N., were given a diet during ten days containing 2.9 grams of protein, 2.7 grams of fat, 10.8 grams of carbohydrate, and in all 81 calories per kilogram of body weight daily. The mineral metabolism as calculated per kilogram of body weight daily was as follows:

MINERAL METABOLISM OF K. ($5\frac{1}{2}$ YEARS OLD, WEIGHT 18.4 KG.) AND OF N. ($7\frac{3}{4}$ YEARS OLD, WEIGHT 23.1 KG.) IN GRAMS PER KG. PER DAY

	Intake		Feces		Urine		Retention	
	K	N	K	N	K	N	K	N
Total ash	0.747	0.697	0.134	0.124	0.469	0.429	+0.144	+0.144
P_2O_5	0.144	0.136	0.049	0.043	0.064	0.064	+0.032	+0.030
CaO	0.060	0.076	0.050	0.042	0.007	0.005	+0.003	+0.029
MgO	0.071	0.065	0.047	0.041	0.010	0.008	+0.014	+0.016
K_2O	0.141	0.136	0.013	0.013	0.116	0.106	+0.012	+0.018
Na_2O	0.346	0.224	0.011	0.012	0.104	0.103	+0.231	+0.110
Cl	0.344	0.324	0.003	0.004	0.309	0.292	+0.032	+0.028

It may be calculated from this table that the older boy took 1.8 grams of calcium oxid in his food daily and retained about 0.07 gram. If the intake had been solely in the form of cows' milk, not far from a liter would have been required.

The question of the calcium content of the diet of children has been the subject of very interesting experiments by Sherman and

[1] Jundel, J.: Nordiskt Medicinskt Arkiv., 1914, **47**, Pt. 2, 1.

Hawley.[1] Twelve children, varying in age between 3 and 13 years, received 750 c.c. of milk in their diet, which contains about a gram of calcium. The calcium retention during a period of 9 days was between 0.15 and 0.62 gm. per day. The allowance of three of these children was then increased to about a liter of milk a day and the average storage of calcium was increased by 70 per cent. When at this point the milk intake was reduced to 500 c.c. and the calcium equivalent of 500 c.c. of milk given in the form of carrots or of spinach, the retention of calcium was not so high as when 1000 c.c. of milk were given. Milk calcium is therefore the best source of calcium for the skeleton of the growing child, and for this and other reasons Sherman is a strong advocate of a liter of cows' milk per child per day. The requirement of phosphate is also met by the ingestion of this quantity of milk.

For nutrition in youth, see page 759.

[1] Sherman, H. C., and Hawley, E.: J. Biol. Chem., 1922, **53**, 375.

CHAPTER XXI

METABOLISM IN ANEMIA AND IN HIGH ALTITUDES

This is the reason why I strive to establish elementary education and professional education upon facts which are true and easily proved to be true. For many people calling themselves *partisans of progress* only see as truth the errors promulgated by education.—CHEVREUL.

IN man one-thirteenth part of the body weight is carried as blood to the lungs at least every minute and there exposed for a period of two seconds to the action of the alveolar air. The blood in the capillaries of the lungs may be estimated as a film 0.01 millimeter in thickness and 150 square meters in area, or nearly a hundred times the area of the surface of the body. Zuntz estimates the combined thickness of the alveolar wall and capillary wall at 0.004 mm. This is the total distance separating the alveolar air from the blood. The gaseous exchange between air and blood is thus readily made possible.

In an experiment by Henriques[1] four different determinations were made upon an anesthetized dog: (1) The rate of flow of blood; (2) the carbon dioxid and oxygen content of the venous blood in the right heart; (3) the quantity of the same gases in the blood of the femoral artery, that is, after the lungs had been traversed, and (4) the extent of the gaseous exchange in the lungs.

The rapidity of the blood flow was 1806 c.c. in three minutes. The following calculations show that no oxidation took place in the lungs or in the blood, and in publishing these results Henriques recants a contrary opinion previously held by him:

	CO_2 C.C.	O_2 C.C.	R. Q.
In 100 c.c. blood of right heart	44.34	2.74	
In 100 c.c. blood of femoral artery	31.55	15.25	
Difference	−12.79	+12.51	
Calculated from 1806 c.c. blood flow	231	226	1.02
Respiration experiment (three minutes)	250	239	1.05
Difference	8 per cent.	5 per cent.	

The differences are within the limits of experimental error. It is evident that the place of oxidation is in the tissues (see p. 31).

[1] Henriques, V.: Biochem. Z., 1915, **71**, 481.

EXPERIMENTAL ANEMIAS

Complete deprivation of oxygen results in asphyxiation and death. The question arises, Will there be any effect upon metabolism if the oxygen supply for the body be reduced? Such a reduction of oxygen available for the tissues might be brought about by bloodletting, anemia, carbon-monoxid poisoning, by life on high mountains, or in balloons at high altitudes, or in pneumatic cabinets at reduced pressure, or by the artificial restriction of the free influx of atmospheric air into the lungs. Any of these methods if carried beyond a certain point is known to produce death.

It was noted by Lavoisier and confirmed by Regnault and Reiset that the respiration of pure oxygen did not increase the metabolism. Liebig was convinced that atmospheric pressure was without influence, for it was evident to him that life at the sea-level was of the same character as on high mountains. In confirmation of these principles Zuntz[1] has definitely shown that if air rich in oxygen be respired, there is an increased oxygen absorption lasting for about one minute, and then the normal quantity is absorbed. The primary increase in the quantity of oxygen absorbed is due to the filling of the lungs with oxygen and a further saturation of the blood with it, processes which are without effect on tissue metabolism. There is apparently no retention of such oxygen within the cells of the organism.

Schaternikoff[2] has compared the metabolism of a normal man of the same age and weight as one suffering from erythrocytosis who had a red blood count of 9,000,000. (Hb. 23 per cent. above the normal.) The normal man inspired 14.65 liters of oxygen per hour, the patient 14.33 liters. The oxygen utilization is therefore dependent on the activity of the cells and not on the oxygen carrying power of the blood.

However, Hill and Flack[3] show that in the fatigue of athletes oxygen inhalation increases the lasting power and decreases the fatigue, probably by maintaining or restoring the vigor of the heart. They believe that the fatigue which follows an athletic feat is mainly cardiac in origin and due to want of oxygen.

Pflüger[4] first showed that frogs could live for a long period in an atmosphere which was free from oxygen when they were main-

[1] Zuntz, N.: Arch. f. Physiol., 1903, Suppl., p. 492.
[2] Schaternikoff, M.: Pflüger's Arch. gesam. Physiol., 1923, **201**, 56.
[3] Hill, L., and Flack, M.: J. Physiol., 1909, **38**, p. xxviii.
[4] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1875, **10**, 313.

tained at a temperature of 0°. After five hours they were capable of movement, and after seventeen hours, although apparently dead, they could be revived when placed in the air. Fletcher and Hopkins[1] have found traces of lactic acid in normal resting frog's muscle, and also traces after a series of muscular contractions which were induced in an atmosphere of oxygen; but they found lactic acid in large quantity in the muscle if the contractions were brought about under anaërobic conditions.

The production of lactic acid under anaërobic conditions has been discussed elsewhere in this volume (pp. 334, 438).

According to Zuntz,[2] any anemic condition which results in the production of lactic acid makes demands on the glycogen reserves of the body, so that sugar may rise abnormally in the blood, and both sugar and lactic acid appear in the urine.

Muscular exertion in man leads to an increase in the quantity of lactic acid in both blood[3] and urine.[4] (See p. 443.)

The discussion of the subject of subnormal oxygen supply may first be considered in connection with bloodletting, which produces an artificial anemia. Bauer,[5] in Voit's laboratory, was the first to study this systematically, and found that the immediate result of bloodletting in the dog was an increased protein metabolism, but that the carbon dioxid elimination was unchanged; 18 to 27 per cent. of the total blood in the body was removed in these experiments.

Hawk and Gies[6] confirm the reports of a higher protein metabolism after bloodletting.

Finkler,[7] in Pflüger's laboratory, withdrew one-third of the total blood from a dog, thereby reducing the rapidity of blood-flow in the femoral artery by one-half, and yet there was no change in the quantity of oxygen absorbed, and, therefore, of the quantity of the carbon dioxid exhaled. Finkler noted, however, that the quantity of oxygen in the venous blood grew constantly less after repeated bleedings. This indicates the interrelation between the oxygen supply and the needs of the tissues. Under ordinary circumstances there are 20 volumes per cent. of oxygen in the arterial blood, of

[1] Fletcher, W. M., and Hopkins, F. G.: J. Physiol., 1906–07, **35,** 247.
[2] Zuntz, N.: "Die Kraftleistungen des Tierkörpers," Festrede, Berlin, 1908, p. 18.
[3] Fries, H.: Biochem. Z., 1911, **35,** 368.
[4] Spiro, P.: Z. physiol. Chem., 1877–78, **1,** 111; Ryffel, J. H.: J. Physiol., 1909–10, **39,** p. xxix.
[5] Bauer, J.: Z. f. Biol., 1872, **8,** 567.
[6] Hawk, P. B., and Gies, W. J.: Am. J. Physiol., 1904, **11,** 226.
[7] Finkler, D.: Pflüger's Arch. gesam. Physiol., 1875, **10,** 368.

which 12 volumes per cent. may return as an unused excess to the right heart. Repeated bleedings by Finkler reduced this percentage in venous blood from 11.80 per cent. to 8.80, 4.06, and 2.71 per cent. The carbon dioxid content of the blood remained unchanged. This decrease in the oxygen content of the blood may stimulate both the heart and respiration to compensatory activity, although nothing resembling asphyxia be present. While the total heat production is unchanged in anemia following bloodletting (except as influenced by increased cardiac and respiratory activity), still it is evident from the diminution of oxygen present in venous blood that there would not be a sufficient supply of oxygen to provide for a largely increased metabolism. Hence the anemic organism is incapable of great muscular work without quick exhaustion accompanied by rapid respiration and heart-beat. These latter are further efforts of compensation for the decrease in the oxygen-carrying elements of the blood.

The removal of blood from a dog, followed by the transfusion of an equal quantity, has no effect upon metabolism,[1] although if an artificial plethora be induced by the intravenous injection of fresh blood into a normal animal, the metabolism is slightly increased, a result which is probably due to increased heart action.[2]

After bloodletting of any considerable magnitude, lactic acid and, it is reported, a small amount of sugar appear in the urine. Thus Araki[3] found lactic acid in the urine of rabbits which had been bled. He also found lactic acid in the urine of rabbits which had been exposed to the action of rarefied air, and he found lactic acid and glucose in the urine of animals the oxygen-carrying capacity of whose blood had been diminished through the respiration of carbon monoxid. It should be noticed in passing that wherever lactic acid is formed in the organism there is a concomitant rise in protein metabolism. Since this lactic acid is a derivative of glucose, its non-combustion may raise the protein metabolism to a higher level, just as is the case when sugar remains unburned in diabetes.

In experimental anemias the hemoglobin content of the blood of rabbits[4] or dogs[5] may be reduced to 20 per cent. of the normal amount, with indications of only slight changes in the intensity of the oxida-

[1] Pembrey, M. S., and Gürber, A.: J. Physiol., 1894, **15**, 449.
[2] Hári, P.: Biochem. Z., 1911, **34**, 111; 1912, **44**, 1.
[3] Araki, T.: Z. physiol. Chem., 1894, **19**, 424.
[4] Eberstadt, F.: Arch. exp. Path. und Pharm., 1912–13, **71**, 329.
[5] Rolly, F.: Deut. Arch. klin. Med., 1914, **114**, 605.

tive processes, and these are usually in the direction of slight increases. Such increases one may interpret as being derived from the rise in protein metabolism and possibly from stimulation of the cells by lactic acid (see p. 383).

Another fact which has been observed by Lewinstein[1] is that when rabbits are kept in a bell-jar at a barometric pressure of 300 to 400 mm. (corresponding to 5000 to 7500 meters above sea-level) they die on the second or third day, and autopsy reveals extreme fatty infiltration of heart, liver, kidney, and diaphragm. These animals took no food. This work has been repeated and confirmed by Rosin[2] who also finds that the fatty livers are almost free from glycogen. The cause of this fatty change, in the present writer's opinion, was the lessened combustion of sugar or its derivative, lactic acid, which lessened combustion always induces an abnormal deposit of fat in any sugar-hungry cells (p. 685).

Laubender,[3] in the climatological laboratory at Davos in Switzerland, has exposed guinea-pigs to atmospheric pressures of 430 and 380 mm. of mercury and found no increase in the oxygen intake. The urinary nitrogen increased, the ammonia elimination increased, and the indications were like those of experimental acidosis.

Experimental anemia by bloodletting also produces lipemia. According to Boggs and Morris[4] the blood fat may rise from 0.3 to 4.53 per cent. of the plasma. Bloor[5] suggests that the cause of this may be due to the forcing out of fat marrow from the stimulation of the function of the blood-forming red marrow of the bones.

Fraenkel and Geppert[6] placed a dog which had fasted seven days under the influence of greatly diminished atmospheric pressure and found an increased protein metabolism which continued on the second and third days. They also suspected the presence of products of incomplete combustion in the urine. These results accord with Araki's investigations.

Von Terray[7] finds no change in the respiratory activity of dogs in air containing between 87 and 10.5 per cent. of oxygen. When 10.5 per cent. of oxygen is present an increased respiratory activity com-

[1] Lewinstein, G.: Pflüger's Arch. gesam. Physiol., 1896–97, **65,** 278.
[2] Rosin, A.: Beiträge path. anat. und allg. Path., 1926, **76,** 153.
[3] Laubender, W.: Biochem. Z., 1925, **162,** 459.
[4] Boggs, T. R., and Morris, R. S.: J. Exper. Med., 1909, **11,** 553.
[5] Bloor, W. R.: J. Biol. Chem., 1925, **63, 1.**
[6] Fraenkel, A., and Geppert, J.: "Ueber die Wirkung der verdünnten Luft auf den Organismus," Berlin, 1883.
[7] von Terray, P.: Pflüger's Arch. gesam. Physiol., 1896–97, **65,** 440.

mences. With 5.25 per cent. of oxygen there is every indication of lack of oxygen for the tissues, and the elimination of lactic acid in the urine is pronounced. The quantity of lactic acid eliminated was greatest after the respiration of an atmosphere containing 3 per cent. of oxygen. The quantities obtained were 1.206, 1.860, 2.176, 2.300, 2.352, 2.663, 3.020, and 3.686 grams of lactic acid in twenty-four hours. In these cases we again see the analogy of the metabolism to that already cited as having been discovered by Araki after bloodletting in rabbits.

Köhler[1] artificially compressed the trachea in the rabbit by tying a lead wire around it. The animal recovered from the operation and lived for four weeks in a condition of dyspnea. Appetite, weight, urine, and body temperature remained normal almost until the end. The dyspnea was apparently insufficient to affect the metabolism. Increased respiration and heart activity were effectual efforts at compensation, so that there was no lack of oxygen in the animal. However, the altered pressure in the lungs and the continued dyspnea brought about a condition of stasis of which the animal died. The secondary alterations were acute and wide-spread, and were hyperemia of the lungs, vesicular and intralobular emphysema of the lungs, and hypertrophy of both sides of the heart.

ANEMIA IN MAN

Pettenkofer and Voit[2] observed the metabolism in an acute case of leucocythemia of four years' duration, and at a time four months before the death of the patient. There was one white to every three red blood-corpuscles, a high degree of anemia, and great physical weakness. The metabolism was exactly the same as in a normal resting man living under the same dietary conditions.

Magnus-Levy states that, rightly interpreted, these experiments of Voit indicate an increased metabolism. He[3] found an increased metabolism in a case of severe pernicious anemia. Grafe[4] was the first to discover large increases in metabolism in leucemia which were proportional to the severity of the disease. Rolly,[5] however,

[1] Köhler, H.: Arch. exp. Path. und Pharm., 1877, **7**, 1.
[2] v. Pettenkofer, M., and Voit, C.: Z. f. Biol., 1869, **5**, 319.
[3] Magnus-Levy, A.: Z. klin. Med., 1906, **60**, 179.
[4] Grafe, E.: Deut. Arch. klin. Med., 1911, **102**, 406; 1922, **139**, 354.
[5] Rolly, F.: *Loc. cit.*

states that in chlorosis and in mild anemias there is no increase in metabolism in human beings.

Meyer and Du Bois[1] made calorimetric observations upon 5 patients suffering from anemia. Direct and indirect calorimetry agreed within 3 per cent. and the respiratory quotients ranged within the normal limits. The following table epitomizes their results:

METABOLISM IN ANEMIA IN MAN

	Type	Hemoglobin in Blood in Per Cent.	Increase in Heat Production above Basal in Per Cent.
Case I.	Splenic	25	8
Case II.	Pernicious	20	24–19
Case III.	Pernicious: transverse myelitis	23–21	33– 7
Case IV.	Pernicious	44	2
Case V.	Pernicious	40	6

These results show an increased metabolism in pernicious anemia which is especially pronounced when the hemoglobin content of the blood falls to 20 per cent. of the normal.

In Case III the legs were wasted and atrophic and could no longer be used. Of itself, this condition would have lowered the metabolism.

Meyer calculated for Case II that there were 3.7 c.c. of oxygen in 100 c.c. of arterial blood. If the patient had had a normal heart-beat of 70 per minute with an output of blood of 50 c.c. per beat, 130 c.c. of oxygen would have been carried to the tissues per minute. In fact, 252 c.c. of oxygen were absorbed by the patient each minute and his pulse-rate was 101. To have supplied enough oxygen for tissue respiration his output of blood per heart-beat must have been at least 66 c.c.

Another patient with lymphatic leucemia had a very high metabolism (+44 per cent.) which was scarcely affected by vigorous *x*-ray therapy, although the lymphocytes were greatly diminished in number.[2]

Riddle and Sturgis[3] state that in myelogenous leucemia there is almost always an increase in basal metabolism. In one case the increase above the normal was 81 per cent. when the myelocytes constituted 65 per cent. of 342,000 white corpuscles. The number of

[1] Meyer, A. L., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 965.
[2] Murphy, J. B., Means, J. H., and Aub, J. C.: *Ibid.*, 1917, **19**, 890.
[3] Riddle, M. C., and Sturgis, C. C.: *Ibid.*, 1927, **39**, 255.

red cells was 2,700,000. Frequently a high basal metabolism was associated with high white blood counts and a low basal with low counts. The general level of the basal metabolism depended therefore on the degree of the elevation of the white blood count, and also on the percentage of immature myeloid cells.

It has been found by Thompkins, Brittingham, and Drinker[1] that the basal metabolism in anemia was invariably lowered on transfusion of blood corpuscles in saline. The pulse and respiratory activity were immediately affected, or at least within 12 hours, whereas the maximum effect upon the metabolism seemed to take place only after a few days.

Bloor and MacPherson[2] state that the blood lipoids in anemia are normal or nearly so, provided the percentage of blood corpuscles remains above half the normal value. At this level the metabolism is also normal.

The characteristic optical properties of human hemoglobin, its power to combine with between 1.33 to 1.35 c.c. of carbon monoxid gas per gram of substance, and its iron content of 0.33 to 0.34 per cent., are always constant, both normally and in diseases such as polycythemia, pernicious anemia, chlorosis, scurvy, and pseudoleucemia. This important fact, which shows that hemoglobin is not itself chemically changed in anemia, was demonstrated by Butterfield.[3]

Aub[4] in a striking piece of work ascribes the fall in metabolism in experimental traumatic shock as a secondary manifestation of the decreased blood flow and as being due to true anoxemia.

In emphysema of the lungs in man determinations by Geppert and by Speck[5] have shown that the respiratory exchange of gases was entirely within normal limits.

Carpenter and Benedict[6] have found the metabolism of a man in whom the left lung was entirely obliterated to be unchanged from the normal.

It is evident from these various citations that the general oxidation of the body is normally maintained in anemia and in pulmonary disease, provided the disturbances are not of extreme intensity.

[1] Thompkins, E. H., Brittingham, H. H., and Drinker, C. K.: Arch. Int. Med., 1919, **23**, 441.
[2] Bloor, W. R., and MacPherson, D. J.: J. Biol. Chem., 1917, **31**, 79.
[3] Butterfield, E. E.: Z. physiol. Chem., 1909, **62**, 173.
[4] Aub, J. C.: Am. J. Physiol., 1920–21, **54**, 388, 408.
[5] Cited by Jaquet, A.: Ergeb. d. Physiol., 1903, **2**, Pt. 1, 562.
[6] Carpenter, T. M., and Benedict, F. G.: J. Biol. Chem., 1909, **6**, p. xv.

METABOLISM IN HIGH ALTITUDES

The constantly increasing use of mountain air as a recuperative force for the worn-out individual leads to the inquiry whether the metabolism at high altitudes is different from that at the sea-level. For knowledge of this sort we were at first indebted to Zuntz and his pupils. The study of the subject may be taken up by using three different methods: First, balloon ascensions; second, the pneumatic cabinet; third, mountain ascents.

The pressure of the atmosphere varies with the height from the sea-level as appears in the following table:

Altitude			Barometer in Mm. Hg.
Meters	Feet	Miles	
0	0	0	760
1000	3,281	0.6	670
2000	6,562	1.2	592
3000	9,843	1.9	522
4000	13,124	2.5	460
5000	16,405	3.1	406
6000	19,686	3.7	358
7000	22,967	4.4	316
8000	26,248	5.0	297
9000	29,529	5.6	

In a celebrated balloon ascension made by Tissandier and two companions in 1875 only Tissandier lived to tell the following tale:

At a height of 7000 meters Tissandier is unable to make the effort to remove his gloves from his pocket. All breathe oxygen. The temperature is $-11°$. Sivel throws ballast. At 7500 meters the condition of torpor is extraordinary, but there is no suffering. The arms cannot be moved to reach for the oxygen tube. At 280 mm. barometric pressure Tissandier wishes to call out that the level of 8000 meters has been passed, but cannot speak. Consciousness is then lost. The height of 263 mm. barometric pressure (28,820 feet) is reached before the balloon begins to descend and, on recovery of consciousness, Tissandier finds that his two companions are dead.

In the graphic words of J. S. Haldane, "Anoxemia not only stops the machine but wrecks the machinery."

Von Schrötter and Zuntz[1] made two balloon ascents to heights of 4560 and 5160 meters. Zuntz showed an increased oxygen absorption of 7 per cent. above that at sea-level. In the case of von Schrötter the increase was slight except during one interval of shivering, when a 20 per cent. increase was recorded. The authors attributed the slight rise in the metabolism to the increased work done

[1] von Schrötter, H., and Zuntz, N.: Pflüger's Archiv. gesam. Physiol., 1902, **92**, 479.

by the respiratory muscles. During the higher ascent sugar appeared in the urine of Zuntz, indicating incomplete oxidation.

The relative composition of the atmosphere is the same at all distances from the earth's surface. Durig and Zuntz[1] find that the atmosphere at a height of 2900 meters contains carbon dioxid 0.03 per cent., nitrogen 79.11 per cent., and oxygen 20.86 per cent., whereas at an altitude of 4600 meters it contains carbon dioxid 0.03 per cent., nitrogen 79.10 per cent., oxygen 20.87 per cent. These are values practically identical with each other and with those determined at sea-level.

LIFE IN PNEUMATIC CABINETS

L. Zuntz[2] found that when he respired in a pneumatic cabinet, at an atmospheric pressure of 448 mm. of mercury there was no change in his respiratory metabolism as compared with the normal. The results may be tabulated as follows:

Per Cent. O_2 in Air	Pressure in Mm. Hg	Respired per Minute	
		O_2 C.C.	CO_2 in C.C.
21	758 mm.	231.25	200.15
12	448 mm.	238.7	213.1

This latter experiment was done at a pressure corresponding to a mountain height of 4500 meters. He also showed that variations in atmospheric pressure within the above limits had no effect on the metabolism during muscular exercise.

This work was repeated by Hasselbalch and Lindhard[3] in an experiment which lasted twenty-six days. During fourteen days a man remained in a pneumatic cabinet at an atmospheric pressure of 455 mm. The consumption of oxygen and the urinary ammonia and amino-acids were unaffected by this influence. (See pp. 589, 594.)

MOUNTAINEERING ON MONTE ROSA

A research of Zuntz[4] on the subject of mountaineering describes how he and Durig ascended to the Col d'Olen (2900 meters), and, having remained there for a week, passed upward to a hut (4560 meters) constructed near the summit of Monte Rosa, the highest mountain of the Alps after Mont Blanc. They lived in this hut two weeks and a half. The height of the barometer was 443 millimeters,

[1] Durig, A., and Zuntz, N.: Arch. f. Physiol., 1904, Suppl., p. 421.
[2] Loewy, A., Loewy, J., and Zuntz, L.: Pflüger's Arch. gesam. Physiol., 1897, **66**, 477.
[3] Hasselbalch, K. A., and Lindhard, J.: Biochem. Z., 1915, **68**, 265 and 295.
[4] Durig, A., and Zuntz, N.: Arch. f. Physiol., 1904, Suppl., p. 417.

which indicates a quantity of oxygen amounting to 12.2 per cent. of an atmosphere. On the Col d'Olen there was no increase in their metabolism when they were resting, and there was no increase in the requirement of energy necessary to accomplish one kilogrammeter of work. This agrees with the results of Bürgi elsewhere mentioned (p. 436). At the higher level, near the summit of the mountain, the resting metabolism increased at once and permanently to the extent of 15 per cent. Zuntz during a former sojourn had noted an increase of 44 per cent. in his metabolism when on the mountain. Exposure to the sunlight was almost without effect on the metabolism. The increased metabolism was not due to cold, for it was present when the individual was in a warm bed in the hut. At sea-level the energy equivalent of 3 kilogrammeters is liberated in the body in order to lift 1 kilogram of body substance 1 meter high. Here on the snow-fields of Monte Rosa Durig required the equivalent of 4.0 to 4.8, Zuntz 5.3 to 6.8 kilogrammeters of energy to accomplish 1 kilogrammeter of work. This agrees with a former experiment of Zuntz when he was living in the same locality, in which he found the increased metabolism necessary to effect 1 kilogrammeter of work in climbing was 70 per cent. above the requirement for the same work at sea-level.

Herxheimer, Wissing, and Wolff[1] state that changing their residence from Berlin to Davos (5111 ft. = 1558 m.) did not appreciably alter the basal metabolism of four individuals. However, on the day of arrival *before exercise* the basal metabolism was represented by an intake of 313 c.c. of oxygen per minute, and *after a rest of 160 minutes* following prolonged exercise on skis, the basal metabolism corresponded to an intake of 356 c.c. oxygen per minute. On repeating the experiment 26 days after arrival, the basal intake at rest was 285 c.c. of oxygen, and 95 minutes after the end of skiing it was 255 c.c. of oxygen. The authors state that the long after-effect of work on metabolism in unacclimated people had been previously overlooked in taking the basal metabolism in high altitudes. This interprets the results of Zuntz given above.

Lippmann[2] states that during residence at Davos the blood volume rises 10 per cent. and the hemoglobin content of the blood increases 20 per cent.

[1] Herxheimer, H., Wissing, E., and Wolff, E.: Z. gesam. exper. Med., 1926, **52**, 447.
[2] Lippmann, A.: Klin. Wochenschr., 1926, **5**, 1406.

The discovery of Viault[1] that at an altitude of 4000 meters the number of red blood-cells increased to 7,000,000 and 8,000,000 per cubic mm. of blood appeared at first to indicate a compensatory increase in oxygen combining power during life in rarefied air. An increase in the quantity of hemoglobin has been positively shown by Zuntz and his co-workers.[2]

While in the high altitudes of Monte Rosa, von Wendt[3] noticed a retention of nitrogen, iron, and potassium which he suggests was in part used for the construction of new red blood-corpuscles, in part for the upbuilding of new musculature.

Hasselbalch and Lindhard,[4] while noting that the ultra-violet rays of the sun reduce the frequency and increase the depth of respiration, find that exposure to the effect of such rays in the high Alps (Brandenburger Hut, 3290 meters) has no effect upon the metabolism (see p. 164). This observation has been frequently confirmed.[5] Children may become appreciably pigmented from ultra-violet radiations without change in basal metabolism.

Not only may the metabolism necessary to accomplish work be greater on high mountains than at sea-level, but the capacity for work is greatly reduced. Schumburg[6] found that he could accomplish a maximum of 999 kilogrammeters of work in one minute in Berlin, 619 when on the Monte Rosa glacier, and only 354 kilogrammeters when he was on the top of the mountain. The limit of work on Monte Rosa was, therefore, one-third of what could be accomplished in Berlin, probably on account of the accumulation of imperfectly oxidized products of metabolism, which reduced the muscular power.[7]

Durig and Zuntz, Mosso, and others have found their respiration to be distinctly of the Cheyne-Stokes character after a return to the hut subsequent to exercise in the higher Alps. They found that when they were on Monte Rosa a temporary oppression resulted if their respiration was partly hindered—as in the case of lacing their boots. Also strict attention to a definite task might reduce the

[1] Viault, F.: Compt. rend. acad. sc., 1890, **111**, 917.

[2] Zuntz, N., Loewy, A., Müller, F., and Caspari, W.: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," Berlin, 1906.

[3] von Wendt, G.: Skan. Arch. Physiol., 1911, **24**, 247.

[4] Hasselbalch, K. A., and Lindhard, J.: *Ibid.*, **25**, 361.

[5] Literature: Flickinger, R.: Deutsch. med. Wochenschr., 1926, p. 1501.

[6] Schumburg, H., and Zuntz, N.: Pflüger's Arch. gesam. Physiol., 1896, **63**, 488.

[7] Lee, F. S.: "Fatigue," "The Harvey Lectures," Philadelphia and London, 1905–06, p. 169.

respiratory activity to such an extent that anemia of the brain, accompanied by dizziness, readily ensued.

The ventilation of the lungs of Durig and Zuntz while at rest at different altitudes varied as follows:

	Respired in Liters per Minute		
	Zuntz Actual	Zuntz Reduced to 760 Mm. Hg and 0° C.	Durig Reduced to 760 Mm. Hg and 0° C.
Sea-level	4.61–5.03	4.15–4.53	5.00–5.63
Col d'Olen	5.97–6.36	3.99–4.16	3.81–5.07
Monte Rosa	6.86–8.52	3.71–4.88	4.05–4.60

The actual amount of inspired air appears to be about the same at different altitudes, an increased volume compensating for increasing rarefaction of the atmosphere.

The atmosphere in which one lives is really the air within the alveoli (Pflüger). Durig and Zuntz have calculated the pressure of oxygen and carbon dioxid within their alveoli at different levels, and, measured in terms of millimeters of mercury, have found them to be as follows:

	Pressures in Mm. Hg			
	Zuntz (of Berlin)		Durig (of Vienna)	
	O_2	CO_2	O_2	CO_2
At home—rest	107	36	109	32
At home—ascending walk	109	33	99	37
On Monte Rosa—rest	57	21	53	24
On Monte Rosa—horizontal walk	60	17	55	21
On Monte Rosa—ascending walk	63	18	55	24

It is evident from a study of the results that muscular exercise in all these localities produces an increase in the alveolar tension of oxygen and a decrease in that of carbon dioxid. This is brought about by the stimulation of respiration.

The lowest recorded oxygen pressure in the alveoli was 48.3 mm. (Durig), and was accompanied by severe headache. A quickened heart-beat produced a more rapid circulation than normal. The experimenters find no ground for believing that there was at any time any real oxygen deficiency in any of the important tissues of the body. They consider that their gradual ascent from sea-level prevented the usual disturbances of appetite and digestion which are probably caused by anemia in the abdominal region (mountain sickness).

In mountain sickness the body temperature may rise to 39° C.[1] or over, a temperature which favors the free dissociation of oxyhemoglobin.[2]

Laquer[3] states that on the summit of Monte Rosa at 3000 meters (456 mm. Hg pressure) there was no increase in the quantity of lactic acid in the blood and therefore no indication of lack of oxygen. In a later paper he[4] describes how he has performed the same amount of work on a bicycle at Frankfort, Davos, and on the Flüela Pass, and determined the lactic acid in the blood immediately after. The lactic acid content of the blood returned to normal after half an hour's rest.

	Height Meters	Lactic Acid in 100 C.C. Blood Mg.
Frankfort a. M.	91	11.4
Davos	1560	27.0
Flüela Pass	2400	28.8

Durig and Zuntz[5] made a voyage to Teneriffe, one of the Canary Islands (situated at about the latitude of Florida), and there ascended a volcano which rises to a height of 3160 meters. They found no essential difference in their metabolism from that at Col d'Olen (2865 meters) except a slight increase due to a quickened rate of respiration which they ascribed to the effect of sunlight.

LIFE ON PIKE'S PEAK

In 1911 the Anglo-American Pike's Peak Expedition, consisting of Douglas, Haldane, Yandell Henderson, and Schneider,[6] spent several weeks on the summit of Pike's Peak with a view to making a thorough study of physiologic adaptation to low atmospheric pressures. The altitude of Pike's Peak is 4290 meters (14,100 feet), which contrasts with the altitude of 4560 meters at which the laboratory on Monte Rosa is located. Pike's Peak, however, differs from Monte Rosa in having a summit which in summer time is almost free from snow, in facility of access by means of a cogwheel railway and in the possession of a very comfortable hotel. The distance from Manitou to the summit is 16.3 kilometers (8.9 miles) by the cog-

[1] Caspari, W., and Loewy, A.: Biochem. Z., 1910, **27,** 405.
[2] Barcroft, J., and King, W. O. R.: J. Physiol., 1909–10, **39,** 374.
[3] Laquer, F.: Z. f. Biol., 1919–20, **70,** 99.
[4] Laquer, F.: Pflüger's Arch. gesam. Physiol., 1924, **203,** 35.
[5] Durig, A., and Zuntz, N.: Biochem. Z., 1912, **39,** 435.
[6] Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C.: Trans. Philosoph. Roy. Soc., 1912, Series B, **203,** 185.

railway and the difference in altitude between the two localities is 2220 meters (7485 feet). Robinson, the resident manager of the hotel, has resided six months each year for seventeen years on the summit and holds the record for the most rapid ascent of the peak, having accomplished it in two hours and thirty-one minutes. This means walking at the rate of 6.5 kilometers (3.5 miles) per hour and ascending at the rate of 906 meters (2974 feet) during the same interval. Since the body weight was 70 kilograms the hourly heat production might have been (see p. 430):

	Kg.-m.	Calories
For lifting the body weight (70 × 906 × 3)	190,260	447
For horizontal forward movement (70 × 0.217 × 6500)	98,735	232
	288,995	679
Add for metabolism standing at rest	.....	88
		767

The requirement of 767 calories per hour exceeds that needed by the trained bicycle rider who rides until exhausted. (See p. 417.)

Contrary to the observations of the Zuntz school, the members of the Pike's Peak Expedition *found no difference in their metabolism on the summit of Pike's Peak from that at sea-level, either during rest or when taking exercise such as walking at the rate of one to five miles per hour. These results were obtained after acclimatization*, and this may account for the difference from those obtained on Monte Rosa.

Thus Schneider[1] has described how the metabolism of a party reacted to the altitude of Pike's Peak. Determinations were made upon men at rest or doing moderate work on a bicycle or walking at the rate of 4 miles per hour. In two of the subjects there was no change in the basal metabolism on arrival on the summit; another subject showed an 18 per cent. increase but was normal after 48 hours. Of five men one only showed a sea-level utilization of energy for work done on the first day. On the third day four of the five men showed a performance of work at the sea-level normal. One man, however, even after 13 days on the mountain, did not return to his low level normal for work, though the low level basal metabolism was present.

Boycott and Haldane[2] had found in experiments on themselves when they were confined in a steel pneumatic cabinet that if the atmospheric pressure was reduced to 356 mm. of mercury, corresponding to a height of 6000 meters (= 20,000 feet) the oxygen pressure in the

[1] Schneider, E. C.: Am. J. Physiol., 1923, **65**, 107.
[2] Boycott, A. E., and Haldane, J. S.: J. Physiol., 1908, **37**, 355.

alveoli fell to 30 mm. and pronounced cyanosis occurred, accompanied first by loss of memory and then by unconsciousness. There was only slight hyperpnea. Greater attenuation of the atmosphere on mountains and in balloons may often be tolerated. This they ascribe to a gradual production of lactic acid within the organism which renders the respiratory center especially sensitive to the stimulus of carbon dioxid. They recommend that one frequently partake of carbohydrates when among the higher mountains in order that a maximum amount of carbon dioxid be furnished to the blood-stream. The carbon dioxid pressure in the alveoli falls as an accompaniment of the rising ventilation. This changed condition of the blood does not pass off at once on return to a lower level.[1] The respiratory stimulus persists and the beneficial effects of descending are promptly felt. At a given altitude on the descent the alveolar oxygen pressure will therefore probably be higher than at the same altitude on the ascent on account of the greater stimulation of the respiratory center.

One may compare the statement of Boycott and Haldane that cyanosis occurred in them when the oxygen pressure in the alveoli fell to 30 mm. with the statement of Loewy and Zuntz[2] that when the oxygen pressure is 31.8 human blood will absorb oxygen so that 56 per cent. of its hemoglobin is saturated. This agrees well with the finding of Ringer[3] in the author's laboratory that dogs lose consciousness when their hemoglobin becomes half-saturated with carbon monoxid gas. Ringer's dogs, however, were not beyond the power of resuscitation until 70 per cent. of the hemoglobin was combined with the poisonous gas.

This observation is similar to that of Bornstein and Müller,[4] who have shown that death occurs when 70 per cent. of the hemoglobin of the blood is converted into methemoglobin by magnesium chlorid. Rapid recovery takes place if the process is not carried so far as this.

The Pike's Peak Expedition already referred to does not fully agree with the interpretations of the Zuntz school. The numerous visitors who reached the summit of Pike's Peak by train and remained only about three-quarters of an hour showed blueness of the lips and cheeks, accompanied by great hyperpnea on exertion. Only a few

[1] Ward, R. O.: J. Physiol., 1908, **37**, 378.
[2] Loewy, A., and Zuntz, N.: Arch. f. Physiol., 1904, p. 214.
[3] Ringer, A. I.: Unpublished.
[4] Bornstein, A., and Müller, Franz: Arch. f. Physiol., 1907, p. 470.

became miserable and faint and required oxygen for their restoration. Among those who arrived on foot, frequently after ten hours of effort, the symptoms were much more severe: nausea, vomiting, headache, and fainting being common. The nose-bleed traditionally assigned as characteristic of life in rarefied atmospheres is mythical. The process of acclimatization is thus outlined: (1) The production of acids which reduce the alkalinity of the blood, this in turn stimulating the respiratory center with a resultant increase in ventilation of the lungs, a fall in the alveolar carbon dioxid tension and an increase in the oxygen tension; (2) an increase up to 150 per cent. of the normal amount of hemoglobin. These factors are of such influence that even more than the normal quantity of oxygen may be carried to the tissues. The hemoglobin was found to be saturated with oxygen to an extent of 95 per cent., which is contrary to the teachings of Zuntz. The authors believe that only adherence to the theory that the alveolar epithelium secretes oxygen from the air into the blood will explain this phenomenon. The pulse and blood-pressure were but little affected. On passing from the summit of the mountain to the sea-level a fortnight is required before the stimulus to the respiratory center disappears and the alveolar carbon dioxid tension becomes normal, and several weeks pass before the total quantity of hemoglobin in the body returns to the normal. It is evident that in unacclimated persons balloon ascents and the like are to a greater extent dangerous to life than in those who have undergone climatic adaptation to high altitudes. Into all phases of the fascinating work of the Pike's Peak Expedition it is impossible to go.

The work was ably supplemented by that of Miss Fitzgerald,[1] who worked among acclimated mine attendants and their wives, persons who had lived a year or more at different heights above the sea-level in Colorado, some of them having been born in these localities. The records included, among others, some made at Denver (5100 ft.), Colorado Springs (6000 ft.), Cripple Creek (10,000 ft.), Camp Bird Mine (11,300 ft.), Lewis (12,500 ft.), and Pike's Peak (14,100 ft.). Miss Fitzgerald showed that for every 100 mm. fall in barometric pressure there was an increase of 10 per cent. above the amount of hemoglobin present in the body at the level of the sea, the law holding true for both sexes. Also, for every fall of 100 mm. in the atmospheric pressure there is a fall of 4.2 mm. in the pressure of

[1] Fitzgerald, M. P.: Trans. Philosoph. Roy. Soc. (London), 1913, Series B, **203**, 351.

alveolar carbon dioxid, accompanied by a progressive fall in the oxygen pressure.

From the facts she makes the following computation:

TABLE SHOWING THE TENSION OF THE ALVEOLAR GASES IN ACCLIMATED INDIVIDUALS

Approximate Altitude When Mean Temperature of Air Column = 15° C.		Atmospheric Pressure	Alveolar Air			
			Percentage		Partial Pressure	
Meters	Feet		O_2	CO_2	O_2	CO_2
		Mm.			Mm.	Mm.
Sea-level	Sea-level	760	14.33	5.58	102.2	39.8
122	400	750	14.26	5.59	100.0	39.2
698	2,290	700	14.17	6.66	92.9	37.1
1326	4,350	650	14.01	5.80	84.5	35.0
2004	6,578	600	13.83	5.95	76.5	32.9
2743	8,999	550	13.62	6.12	68.5	30.8
3552	11,653	500	13.36	6.34	60.5	28.7
4447	14,589	450	13.05	6.60	52.6	26.6
5445	17,864	400	12.64	6.94	44.6	24.5
6579	21,584	350	12.10	7.39	36.7	22.4
7889	25,882	300	11.34	8.02	28.7	20.3
9437	30,960	250	10.24	8.97	20.8	18.2

Each successive diminution of 100 mm. of barometric pressure causes a greater absolute increase in the ventilation of the lung and this introduces more oxygen. The full reaction, however, is not effected in short periods. Thus, in the experiment by Boycott and Haldane (see p. 589) in which they subjected themselves to a barometric pressure of 350 mm., their alveolar carbon dioxid tensions were 31.2 and 27.3 mm. respectively. In an acclimatized individual the carbon dioxid tension at this level of the barometer would have been 22.4 mm. and he would have had 3.2 per cent. more oxygen in his alveoli than Haldane had. Acclimatization involving this reaction, as well as increasing the quantity of hemoglobin, would have prevented the cyanosis and unconsciousness which followed in the experiments of Boycott and Haldane when they were in the respiration chamber.

LIFE IN THE PERUVIAN ANDES

In Peru a railway ascends the slopes of the Andes to Cerro del Pasco, a mining town of 12,000 inhabitants located at a height of 14,200 feet and yet below the snow line. This is "the highest altitude at which a population is maintained and carries on the ordinary functions of life." Another Anglo-American expedition

under the leadership of Barcroft[1] spent several weeks observing conditions of life in this community. No one, whether a newcomer or a native whose ancestors have lived at Cerro for generations, can do the amount of physical work that he could accomplish at ordinary altitudes. One gets out of breath rapidly in the effort of climbing a hill and there is a tendency to shift from a continuous to a spasmodic type of effort. There is apparently a tendency to accumulate an "oxygen debt" in the sense of Hill (see p. 442). Even the native porters, carrying ore up steps in a mine, progress very slowly, their respiration is labored, and can be heard far down the stairway. The pulse rate is markedly accelerated as the result of exercise.

The lips and nails of all residents were cyanotic, their faces plum color. Half a minute's respiration of oxygen gas changed the color of the faces of both visitors and natives. During exercise the lips became blue probably because of a diminished saturation of arterial blood. Arterial blood darkens at this time. There was never any great difference between the oxygen tension of arterial blood and that of the alveolar air. Four acclimatized Anglo-Saxons showed an average oxygen pressure of 52 mm. in arterial blood and of 56 mm. in their alveolar air. At the sea level the hemoglobin would be 95 per cent. saturated; at Cerro it was 82 to 85 per cent. saturated, which sufficiently accounts for the plum color of the face.

The compensating influence exerted by the increased respiration is illustrated as follows:

	Alveolar Pressure	
	O_2 Mm. Hg	CO_2 Mm. Hg
Sea level	100	40
14,200 feet (same volume of respiration)	38	40
At actual volume of respiration	55	28

The average basal metabolism of six persons at the sea level was 62.8 calories; at Cerro 64.3 calories, and the resting pulse rate was unchanged. Four of the eight visitors on their arrival had to go to bed from mountain sickness, but after acclimatization all could work in the laboratory 8 to 9 hours a day.

The reaction of the blood plasma was unaltered. In twelve natives the hemoglobin value of the blood was always above the normal.

	Hemoglobin Value (Sea Level = 100)				
	150	149–140	139–130	130–120	Below 120
Number of natives	1	3	4	4	None

[1] Barcroft, J., Binger, C. A., Bock, A. V., Doggart, J. H., Forbes, H. S., Harrop, G., Meakins, J. C., and Redfield, A. C.: Philosoph. Trans. Roy. Soc. (London), 1923, B, **211**, 351–480.

The actual factors of acclimatization are thus summarized:

1. Increase in total ventilation which raises alveolar oxygen tension 10 to 12 mm. higher than it otherwise would have been.

2. Rise in the oxygen dissociation curve so that at any oxygen pressure the hemoglobin will take up more oxygen than before.

3. Rise in the number of red blood corpuscles and the amount of hemoglobin.

During exercise the hydrogen ion concentration of the blood rises higher than at the sea level, hence the urgency of the breathlessness. Barcroft (with C. D. Murray) describes the process by which the oxygen dissociation curve of hemoglobin rises. The increased ventilation of the lung causes an elimination of CO_2 from the blood, tending to induce alkalosis which is compensated for by the migration of chlorids from the corpuscle, and this maintains the normal reaction of the plasma while the corpuscle, having lost both carbonic acid and chlorids, is more alkaline and therefore takes up oxygen more readily.

The laboratory experiment of Barcroft[1] which led up to the Peruvian experience was one in which a subject lived in a pneumatic cabinet 6 days at low atmospheric pressures. On the 6th day when the partial pressure of oxygen was 86 mm., corresponding to a height of 18,000 feet, the resting alveolar air contained oxygen at a pressure of 46 mm., carbon dioxid at a pressure of 35 mm. At this pressure the blood would have been 83 per cent. saturated and dark in color. On withdrawing a sample of the blood it *was* dark in color. During both rest and exercise on a bicycle the tension of oxygen in the blood was less than the tension of oxygen in the alveolar air. Hence *secretion of oxygen through the alveolar wall is not a factor in acclimatization.*

"THE EPIC OF MOUNT EVEREST"

The conquest of Everest (8840 meters = 29,000 feet = 5.5 miles), the highest Himalayan mountain, has been accomplished with certainty within 800 feet, and no one will ever know whether Mallory and Irvine reached the summit of the earth. Two members of the expedition a few days before Mallory's attempt slept at 27,000 feet, and one of the two climbed to a height of 28,126 feet without the aid of carried oxygen. It required 1 hour to go a distance of 300 yards and make 100 feet of ascent. Seven to ten complete respirations

[1] Barcroft, J., Cooke, A., Hartridge, H., Parsons, T. R., and Parsons, W.: J. Physiol., 1919–20, **53**, 450.

were necessary for each step forward, with rest for a minute or two every 20 or 30 yards to recover from panting. Somervell,[1] who was one of this party, reports that while climbing at this height the pulse rate was 160 to 180 per minute and the respiration rate 50 to 55 per minute. Their minds were clear, temper and resolution fairly good. The blood pressure suffered no change, but all who went over 27,000 feet had dilated hearts.

Chocolate and biscuits were eaten as a duty, but in this high dry air pemmican soup and coffee alone were relished. Liquids were a primary need. Somervell reports the following values for alveolar oxygen:

	Altitude	Barometer	Number of Subjects	Alveolar O_2 Tension
	Ft.	Mm.		Mm.
Base camp	16,500	425	5	48–58
High camp	23,000	330	4	37–39
Later, same base camp	16,000	425	2	54–56

For the summit of Mount Everest (barometer = 260 mm.) a value of 23 mm. pressure for alveolar oxygen has been calculated. Although it is possible that life may be maintained by the acclimated at this level, yet the physical effort of work amid snow and rock seems to call for superhuman endurance. The physiologically possible may be physically impossible. Yet failure to accomplish the ascent was attributed to bad weather and also to fatigue endured in extraordinary exertion expended in the rescue of the lives of four native porters a few days previously.

For convenience the altitudes which have been considered may here be tabulated.

Laboratory	Altitude	Barometer	Partial O_2 Pressure
	Ft.	Mm.	Mm.
Oxford	0	760	160
La Canadas (Teneriffe)	7,000	590	124
Col d'Olen	10,000	530	111
Teneriffe (summit)	12,000	495	104
Pike's Peak	14,000	465	98
Cerro	14,200	458	96
Monte Rosa (Margharita hut)	15,000	445	94
Experimental chamber (Barcroft)	18,000	398	84
High camp, Himalayas	23,000	330	70

[1] Somervell, T. H.: J. Physiol., 1925, **60**, 282.

At the risk of over-emphasis of this interesting field of human endeavor, one may cite the experiments of Schneider, Truesdell, and Clarke.[1] These authors found, when men were placed in rarefied air in pneumatic cabinets, that the oxygen absorption was first reduced, then was raised by the phenomenon of mountain sickness, and finally in $3\frac{1}{2}$ to 8 hours, when acclimatization began to develop, the basal metabolism returned to normal. The immediate effects 30 to 60 minutes after reducing the pressure appear in the following table:

	Sea Level	10,000 Ft. 528–535 Mm.	15,000 Ft. 443–450 Mm.	20,000 Ft. 371–378 Mm.	25,000 Ft. 312 Mm.
Minute volume in liters	6.8	8.0	7.4	8.9	11.9
O_2 in c.c.	256	261	240	232	239
CO_2 in c.c.	221	213	200	204	216
R. Q.	0.86	0.82	0.84	0.88	0.90

AN AIRPLANE FLIGHT

Schneider and Clarke[2] have determined the tension in the alveolar air of five men, who made 14 flights and reached an altitude of 15,000 feet, usually in 45 minutes.

	Alveolar O_2 Tension Mm.	Hemoglobin Saturation Per Cent.
Sea level	100.5	96
On reaching 15,000 feet	49.8	82
15 minutes later at 15,000 feet	56.6	86

The strong action of the wind stimulates the respiratory activity and therefore gives a higher degree of ventilation than at the same height without wind. Compare these values with those at the "base camp" on Mount Everest.

The results of these varied experiments confirm the independence of the metabolism of variations in atmospheric pressure as regards all the customary habitats of mankind. The beneficial properties of mountain air may be largely the same as those derived at watering-places, *i.e.*, outdoor life, cool air, exercise, diversion through change of scene, mental rest, and, finally, suggestion of benefits received. The dry, crisp air undoubtedly benefits catarrhal disturbances, which are, on the other hand, aggravated by the climate of the sea-shore.

Gigon[3] states that one who has once lived at an altitude of 1800 meters can return there as an old man better than one who has never in his life left the sea level.

[1] Schneider, E. C., Truesdell, D., and Clarke, R. W.: Am. J. Physiol., 1924, **70**, 283.
[2] Schneider, E. C., and Clarke, R. W.: *Ibid.*, 1926, **76**, 354.
[3] Gigon, A.: Verhandl. d. klimat. Tagung in Davos, 1925.

CHAPTER XXII

THE INFLUENCE OF THE THYROID

The day of the genius in the garret has passed, if it ever existed. A host of men, great equipment, long, patient, scientific experiment to build up the structure of knowledge, not stone by stone, but grain by grain, is now our only sure road of discovery and invention.—HERBERT HOOVER.

THE literature regarding the action of the internal secretions upon metabolism is very large. Much of it is crudely unscientific. Where several unknown factors are interacting, as happens in this field of study, it is pleasant to give the fancy full play, and this is also a perfectly harmless occupation provided such mental activity does not develop into hallucination. Du Bois, in writing concerning exophthalmic goiter, makes the ironical proposal, "For the purpose of simplicity in this paper one may consider the symptoms of exophthalmic goiter to be caused by hypersecretion of the thyroid, and allow the reader to select for himself those cases in which he believes other glands to be involved."

Thus Fitz,[1] after a study of the literature and the cases treated at the Mayo Clinic, finds that hyperthyroidism and diabetes occur together in the same person in a small number of cases, but he finds no evidence that such occurrence is more than chance.

The thyroid gland is a gland whose internal secretion profoundly affects the amount of general metabolism. No other gland compares with it in this regard. This influence is brought about by an iodin-containing substance called thyroxin (see p. 237) which, when produced in normal quantities, maintains the proper functions of the body. A subnormal production reduces the quantity of metabolism. An overproduction raises the metabolism. Myxedema is a condition in which the thyroid gland has atrophied and its secretion is no longer available. Exophthalmic goiter presents the opposite phase, since here a superabundance of thyroxin is believed to be produced. Symptoms somewhat akin to the latter condition may be induced in normal animals and man by ingesting thyroid extracts. The

[1] Fitz, R.: Arch. Int. Med., 1921, **27**, 305.

essential iodin content of a man weighing 70 kg. has been placed at 28 milligrams. (See p. 606.)

It has been noted by Stoklasa[1] that a growing beet root may evolve twice the amount of carbon dioxid if placed in a soil containing iodin than if no iodin be present. The iodin promotes the oxidative destruction of glucose. Gudernatsch[2] has fed young tadpoles with thyroid extracts and witnessed their early metamorphosis into pigmy frogs. It has been found that lack of iodin in the dietary of hogs in the northwestern states is the cause of the "hairless pig malady," that is, the birth of weaklings, without hair, which die early. Administration of iodin cured the disease and saved the farmers' livestock.[3]

More important was the saving of the children of the same locality from goitrous affections. Kimball and Marine[4] found that in man, after giving iodin, one-third of the cases of uncomplicated simple goiter disappeared or were markedly reduced. Simple goiter depends upon the absence of iodin in the diet. On account of the absence of iodin in the soil endemic goiter existed in the Great Lakes Basin and the St. Lawrence River valley.

When Marine[5] gave 2 gm. of sodium iodid each spring in 0.3 gm. doses daily to 2190 school children at Akron, Ohio, only 5 developed thyroid enlargements, while of 2305 children who did not take iodin, 495 developed goiter. In Switzerland 1 to 5 mg. taken daily in table salt protects the population.

Olin[6] states that among certain groups of recruits from northern Michigan and Wisconsin as many as 30 per cent. of the men were found to be disqualified for army service by toxic goiters. At Houghton, Michigan, two-thirds of 13,725 children had goiter. A chocolate tablet containing 10 mg. of sodium iodid, given weekly, prevented the goitrous condition.

It is an important fact that iodin ingestion may afford relief to patients suffering from exophthalmic goiter. Plummer[7] and Plummer and Boothby[8] established this. Quite large doses of iodin (in Lugol's solution) lowered the metabolism, decreased the severity of

[1] Stoklasa, J.: Biochem. Z., 1926, **176,** 38.
[2] Gudernatsch, J. F.: Am. J. Anat., 1913, **15,** 431.
[3] Hart, E. B., and Steenbock, H.: J. Biol. Chem., 1918, **33,** 313.
[4] Kimball, O. P., and Marine, D.: Arch. Int. Med., 1918, **22,** 41.
[5] Marine, D.: *Ibid.*, 1923, **32,** 811.
[6] Olin, R. M.: J. Am. Med. Assn., 1924, **82,** 1328.
[7] Plummer, H. S.: *Ibid.*, 1923, **80,** 1955.
[8] Plummer, H. S., and Boothby, W. M.: J. Iowa Med. Soc., 1924, **14,** 66.

the clinical symptoms, and rendered operative procedures relatively safe. It has been suggested by Kendall that thyroxin, without the normal number of iodin atoms, might produce the toxic symptoms which aggravate the patient's condition. Means quotes Trousseau[1] as describing a patient to whom he inadvertently prescribed tincture of iodin instead of tincture of digitalis and who reacted with a fall in the pulse rate from 150 to 90 beats a minute.

Starr, Walcott, Segall, and Means[2] confirm the finding of Plummer that administration of iodin by mouth will bring about an abrupt remission in most cases of exophthalmic goiter, a remission often as rapid and as extensive as that following sub-total thyroidectomy.

EXTIRPATION OF THE THYROID

Sutherland Simpson[3] has extirpated the thyroid in one of twin lambs, with the following results: (1) increased susceptibility to infections, as in human subjects; (2) growth much retarded, the thyroidectomized animal having one-half to one-third the weight of the normal twin; (3) body temperature subnormal; (4) animal dull, stupid, unresponsive; (5) fleece becomes ragged and tends to fall out, horn growth greatly affected; (6) if pregnancy occurs the fetus dies in utero or survives birth only a few hours; (7) the blood sugar is subnormal; (8) there is no effect on the development of the pituitary or parathyroid glands; also (9) removal of the thyroid in adult sheep has no deleterious effect.

The symptoms listed above are characteristic of cretinism.

The subcutaneous injection of small amounts of thyroxin caused a large increase in the neuromuscular activity of thyroidectomized sheep, even during extreme lethargy and muscular weakness. This revival occurs after a latent period of 3 to 8 days.[4]

The Protein Metabolism.—Fritz Voit[5] found, after administering thyroid extracts to a dog, that there was an increase in total metabolism and also in the quantity of protein destroyed. Thyroidectomy, as Janney[6] showed, causes little change in the urinary nitrogen in the

[1] Trousseau, A.: Lect. on Clin. Med., 1868, vol. 1, p. 587. Publ. of New Sydenham Society.

[2] Starr, P., Walcott, H. P., Segall, H. N., and Means, J. H.: Arch. Int. Med., 1924, **34**, 355.

[3] Simpson, S.: Quart. J. Exper. Physiol., 1924, **14**, 161, 185, 199.

[4] Liddell, H. S., and Simpson, S.: Am. J. Physiol., 1925, **72**, 63.

[5] Voit, F.: Z. f. Biol., 1897, **35**, 116.

[6] Janney, N. W., and Isaacson, V. I.: Arch. Int. Med., 1918, **22**, 174.

dog. The injection of thyroxin into a normal dog raised the fasting urinary nitrogen from 3.4 to 4.75 gm. and the following day to 5.52. Glucose ingestion reduced this to 4.82 and 5.07 gm. and then, after stopping the carbohydrate, the nitrogen rose to 7.26 gm. "A veritable metabolic storm broke loose." A similar reaction takes place in man (see p. 359).

Lánczos[1] says that in fasting thyroidectomized dogs there is no "premortal rise" in protein metabolism.

In the thyroidectomized dog the usual increases in protein metabolism which follow the administration of phlorhizin[2] or which follow partial asphyxia[3] do not occur.

The Blood Sugar.—Janney and Isaacson[4] investigated the blood sugar curves in dogs before and after thyroidectomy. Hypoglycemia was characteristic of thyroidectomized dogs and after the ingestion of glucose the blood sugar did not rise so high as it does in the normal animal, but the rise was more prolonged. Mark[5] confirms this and finds that in animals treated with thyroid preparations the ingestion of glucose causes a very high degree of hyperglycemia.

When thyroid extracts are given to rabbits and dogs the liver contains less glycogen than normally.[6] All these experiments at least indicate that excess of thyroid extract prevents the liver from holding glycogen in the normal fashion, or that glycogen is oxidized more rapidly than usual; whereas in cretinism the liver would appear to be especially capable of retaining glycogen. The reaction of the blood sugar in thyroid disease would be explicable on this theory.

The Action of Thyroxin on Tissue.—Aub, Bright, and Uridil[7] report that, although urethan anesthesia does not materially affect the basal metabolism of cats, thyroxin administered to such animals raises the metabolism. Hence this increased basal metabolism cannot be explained by increased muscular activity, muscular fibrillation, or increased muscle tonus. Also prior removal of the adrenals does not lessen the effect of thyroxin. Hence thyroxin, by itself, directly stimulates resting cells to a higher level of oxidation.

[1] Lánczos, A.: Biochem. Z., 1926–27, **179,** 186.
[2] Lusk, G.: Proc. XVII Internat. Cong. Med. (London), 1913, Sec. II, p. 13.
[3] Mansfeld, G.: Pflüger's Arch. gesam. Physiol., 1915, **161,** 502.
[4] Janney, N. W., and Isaacson, V. I.: Arch. Int. Med., 1918, **22,** 160.
[5] Mark, R. E.: Pflüger's Arch. gesam. Physiol., 1926, **211,** 523.
[6] Parhon, M.: J. de physiol. et de path. gén., 1913, **15,** 75; Cramer, W., and Krause, R. A.: Proc. Roy. Soc. (London), 1913, B, **86,** 550.
[7] Aub, J. C., Bright, E. M., Uridil, J.: Am. J. Physiol., 1922, **61,** 300.

Opposed to this conception is the work of Abderhalden and Wertheimer.[1] These authors have paralyzed the sympathetic nervous system by administering ergotamin to rats. This causes a fall in metabolism (compare p. 119). If now thyroxin be administered, there is no increase in metabolism such as occurs in control animals. The conclusion is drawn that thyroxin acts on the sympathetic nervous system.

Asher and Horrisberger[2] find that administration of thyroid tablets to phlorhizinized rats may cause an increase of 183 per cent. in the consumption of oxygen, the respiratory quotient being 0.71. Hence carbohydrate oxidation is not necessary in the reaction.

EXOPHTHALMIC GOITER AND MYXEDEMA

It was Janney[3] who first showed that administration of a therapeutic dose of thyroxin (optimal, 0.75 mg. daily) may bring about not a loss but an actual gain in body nitrogen. He pointed out that there was an anabolic and therapeutic action as distinguished from a catabolic and toxic action, and that in the cretin there is a failure of normal repair and growth processes which are controlled by the thyroid. Even in exophthalmic goiter, he said, small doses of thyroxin do not prevent a positive nitrogen balance, though there is no therapeutic effect.

Recent experiments by Lauter and Jenke[4] show that in a patient with exophthalmic goiter, who had a high basal metabolism, the administration of carbohydrate in large quantity in a protein-free diet reduced the protein metabolism to the level of the wear and tear quota, just as in a normal individual. However, it must be remembered that Deuel reduced his protein metabolism to the wear and tear level of about 2 gm. of urinary nitrogen and then, after a large dose of thyroxin, found 6 gm. of nitrogen in the urine on the sixth day after giving the autacoid (see p. 359), a result comparable to that of Janney in experiments upon a dog.

Boothby writes, "A patient with exophthalmic goiter, while passing through a stage which may be termed gastrointestinal crisis associated with nausea, vomiting, diarrhea, and inability to retain food is, of course, like any starving individual in a state of negative nitrogen balance."

[1] Abderhalden, E., and Wertheimer, E.: Pflüger's Arch. gesam. Physiol., 1927, **216**, 697.
[2] Asher, L., and Horrisberger, W.: Biochem. Z., 1921, **121**, 64.
[3] Janney, N. W.: Arch. Int. Med., 1918, **22**, 187.
[4] Lauter, S., and Jenke, M.: Deut. Arch. klin. Med., 1925, **146**, 323.

The Blood Sugar.—Geyelin[1] discovered low blood-sugar values of 0.05 and 0.068 per cent. in myxedema, and he demonstrated the presence of hyperglycemia in 90 per cent. of the cases of hyperthyroidism. After giving glucose there was a delay in the fall of the curve of blood sugar.

The rapidity with which glucose may be used as fuel in hyperthyroidism is shown by Sanger and Hun[2] in their comparison between the reaction of patients and of normal persons to the administration of 1.75 gm. of glucose per kg. of body weight.

	Normal Controls	Hyperthyroidism
Fasting:		
Blood sugar, gm. per liter	0.085	0.099
R. Q.	0.80	0.76
60 minutes after glucose:		
Blood sugar, gm. per liter	0.134	0.202
R. Q.	0.84	0.91

Of about 100 gm. of glucose administered 18 per cent. was oxidized in two and one-half hours by the controls and 36 per cent. by the patients. The actual rise in total metabolism was the same in both groups, and hence the specific dynamic action of glucose was the same. There were ten persons in each group.

Richardson, Levine, and Du Bois[3] believe that the storage of glycogen in exophthalmic goiter in man is quite normal. In one patient whose metabolism was 86 per cent. above the basal level it was found that the respiratory quotient fell to 0.75 after 51 hours without food, and acidosis was present, as would happen normally when the quotient was 0.75 (see p. 665). The higher metabolism incurs a greater combustion of carbohydrate than usual.

It appears, therefore, that the work with experimental animals is not strictly in accord with the findings in exophthalmic goiter, as regards protein metabolism and glycogen content of the liver.

THE RESPIRATORY METABOLISM IN EXOPHTHALMIC GOITER

Freidrich Müller[4] reports a case of exophthalmic goiter in an individual weighing only 29 kilograms who constantly lost weight notwithstanding a daily diet containing 68 grams of protein with 58 calories per kilogram.

Magnus-Levy[5] found the carbon dioxid output increased after giving a normal man thyroid extracts.

[1] Geyelin, H. R.: Arch. Int. Med., 1916, **16,** 975.
[2] Sanger, B. J., and Hun, E. G.: *Ibid.*, 1922, **30,** 397.
[3] Richardson, H. B., Levine, S. Z., and Du Bois, E. F.: J. Biol. Chem., 1926, **67,** 737.
[4] Müller, F.: Deut. Arch. klin. Med., 1893, **51,** 361.
[5] Magnus-Levy, A.: Berliner klin. Wchnschr., 1895, **32,** 650.

Magnus-Levy[1] found an increased oxygen intake in cases of exophthalmic goiter amounting to 22, 42, and 70 per cent. above the normal.

Steyrer[2] made interesting experiments on the metabolism in this disease. The patient was twenty-one years old, temperature normal; the total metabolism during two days was determined twice at intervals one month apart and while the person was resting in bed. During the second period the disease had made considerable progress, the patient having a hot skin and being in a highly nervous state.

	Day	Calories of Metabolism	Weight in Kg.	Calories per Kg.
Period I	1	2665	45.1	59.1
	2	2731	46.4	58.9
Period II (one month later)	1	3666	48.2	76.1
	2	3318	47.5	69.9

Calorimetric studies upon 12 thyroid cases have been made by Du Bois[3] and the literature has been very fully considered by him. The accompanying table epitomizes the results obtained by Du Bois with 3 cases of exophthalmic goiter and with 1 cretin thirty-six years of age.

THE METABOLISM OF 3 PATIENTS WITH EXOPHTHALMIC GOITER AND OF 1 CRETIN

Subject and Date	Character of Experiment	Pulse-rate	Calories per Sq. Meter, Du Bois Formula	Per Cent. Rise above Normal Basal of 39.7 Cal.	Per Cent. Rise above Patient's Own Basal	R. Q.
Case I:						
Feb. 16, 1914.	Basal	137	69.4	+75	....	0.76
Feb. 20, 1914.	Basal	111	63.7	+60	....	0.77
Feb. 21, 1914.	Glucose, 100 gm.	105	68.8	....	+ 9	0.94
Feb. 25, 1914.	Casein, N = 8.9 gm.	138	71.9	....	+14	0.83
April 24, 1914.	Basal	120	60.9	+53	....	0.78
April 23, 1915.	Basal, one year later	99	57.7	+45	....	0.77
Case II:						
March 22, 1915.	Basal	107	59.4	+50	....	0.79
May 11, 1915.	Basal two weeks after ligating arteries	134	71.2	+79	....	0.76
Case III:						
March 12, 1915.	Basal	100	74.4	+87	....	0.78
Case XII (Cretin):						
April 10, 1914.	Basal	84	33.0	−17	....	0.92
April 14, 1914.	Glucose, 100 gm.	88	37.9	....	+15	1.00
April 21, 1914.	Casein, N = 3.6 gm.	82	34.9	....	+13	0.93
April 23, 1914.	Basal	78	31.0	−22	....	0.87
May 1, 1914.	After thyroid extract	95	39.8	+ 0	+28	0.79

[1] Magnus-Levy, A.: von Noorden's "Handbuch der Pathologie des Stoffwechsels," Berlin, 1907, **2**, p. 325.

[2] Steyrer, A.: Z. exp. Path. und Therap., 1907, **4**, 720.

[3] Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 915.

The total difference between direct and indirect calorimetry in the 12 cases was 2.9 per cent.

The specific dynamic action of protein and glucose was within the normal limits, and glucose was oxidized in an entirely normal fashion, even in the presence of some glycosuria. In one experiment (Case I) 89 per cent. of the energy production was derived from glucose.

Forschbach and Severin,[1] in Minkowski's clinic, state that the administration of 100 grams of glucose in exophthalmic goiter does not invariably produce glycosuria. It is possible that the glycosuria may be due to a difficulty of glycogen retention in hyperthyroidism.

The rapid oxidation of carbohydrate due to the high metabolism is the probable explanation of the fact that the respiratory quotients found during the determinations of the basal metabolisms of patients with hyperthyroidism invariably show a lower average level than the normal.

Du Bois finds that the height of the metabolism gives the best index of the severity of the disease and classifies very severe cases as showing an increase of 75 per cent. above the normal heat production, severe cases as showing over 50 per cent., and moderately severe and mild cases as showing less than 50 per cent. increase above the normal basal metabolism. Rest of a week in bed usually caused a 10 per cent. fall in metabolism. Thyroid sera, ergotin, and quinin hydrobromate had little effect. Ligation of the thyroid arteries was followed by a rise in metabolism in most cases. There was no indication that any conservative form of treatment was more effective than mental and physical rest.

Means writes "It was not until after the publication of the surface area formula of the Du Boises in 1916 that the calorimetry of thyroid cases became a common clinical procedure."

Means and Aub[2] state that the safest treatment of exophthalmic goiter is the routine irradiation of the thyroid and thymus glands in all cases, with surgery held in reserve for patients who do not then do well. They state that in the management of exophthalmic goiter periodic determinations of the basal metabolism should be quite as much a matter of routine as is the examination of urine for sugar in diabetes mellitus. In a later paper Means and Holmes[3] affirm that in two-thirds of the cases of toxic goiter the use of the *x*-ray brings

[1] Forschbach, J. and Severin, J.: Arch. exp. Path. und Pharm., 1914, **75**, 168.
[2] Means, J. H., and Aub, J. C.: Arch. Int. Med., 1919, **24**, 645.
[3] Means, J. H., and Holmes, G. W.: *Ibid.*, 1923, **31**, 303.

about either recovery or improvement. Thyroid tissue may thus be destroyed and the metabolism may be reduced from +50 per cent. of the normal to the normal level. There is a fair degree of coördination between the pulse rate and the height of the metabolism in exophthalmic goiter[1] and from this Minot and Means[2] infer that the tachycardia is chiefly the result of the increased metabolism.

In myxedema the metabolism is reduced and there is a fall in body temperature. Andersson[3] reported a case of a woman whose metabolism was as low as 1260 calories or 18.8 per kilogram: after treatment for nine months with thyroid extracts the heat production rose to 2099 calories, or 32.3 per kilogram. These latter are normal values. The temperature rose to normal with the increase in metabolism.

The cretin investigated by Du Bois (see table on p. 603) had a basal metabolism which was 20 per cent. less than the normal adult. Response to the specific dynamic action of food was normal. The individual, by Binet's tests, had the mentality of a child of seven years, though his age was thirty-six. This condition is a rare example in which the metabolic processes are permanently depressed.

Means and Aub[4] report the basal metabolism in five typical cases of hypothyroidism:

		Metabolism Per Cent.
Case	I Myxedema	−33
"	II Cretinism	−19
"	III Cachexia strumipriva	−15
"	IV Myxedema	−25
"	V "	−18

Means and Burgess[5] conclude that if fever, acromegaly, leucemia, and anemia be excluded, the finding of a high basal metabolism is strong presumptive evidence of hyperthyroidism. In a similar manner, after the exclusion of starvation, hypopituitarism, and hypoadrenalism, a low basal metabolism is strong presumptive evidence of hypothyroidism.

A classical experiment by Boothby[6] shows that after administering 16 mg. of Kendall's thyroxin to a myxedematous and apparently thyroidless patient with a metabolism 30 per cent. below the normal the metabolism gradually rose to a maximum and then gradually fell

[1] Sturgis, C. C., and Tompkins, E. H.: Arch. Int. Med., 1920, **26,** 467.
[2] Minot, G. R., and Means, J. H.: *Ibid.*, 1924, **33,** 576.
[3] Andersson, J. A.: "Hygiea," Stockholm, 1898, **60,** (quoted in R. Tigerstedt's "Lehrbuch der Physiologie," Leipzig).
[4] Means, J. H., and Aub, J. C.: Arch. Int. Med., 1919, **24,** 404.
[5] Means, J. H., and Burgess, H. W.: *Ibid.*, 1922, **30,** 507.
[6] Boothby, W. M.: J. Am. Med. Assn., 1921, **77,** 252.

to the original level after a period of about 6 weeks. The 16 mg. of thyroxin caused the production of 16,125 calories above the quantity which this patient otherwise would have produced. This is the equivalent of the heat which would have been liberated in the oxidation of 4.25 kg. of glucose. In the words of Plummer, thyroxin is "a catalyst that accelerates the formation of a quantum of potential energy in the cells of the organism." A milligram of thyroxin, the

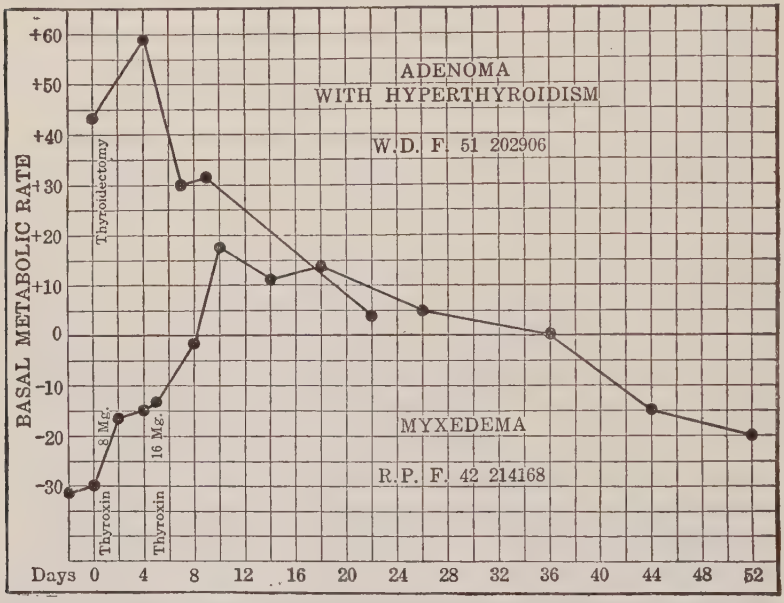


Fig. 40.—On the upper curve the basal metabolic rates of a patient having adenoma with hyperthyroidism are plotted showing the original preoperative rate and the immediate postoperative rise in the metabolic rate, followed by the drop to normal after partial thyroidectomy. The lower curve illustrates the effect on the metabolic rate of a myxedematous patient of two intravenous injections of 8 and 16 mg. of thyroxin, from which can be calculated the amount of thyroxin needed to bring such a patient to a normal metabolic rate; and therefore the presumable amount of thyroxin in the body, and also the rate at which the thyroxin is destroyed or eliminated (Boothby).

most powerful agent influencing metabolism, may be responsible for an increase in the heat production equal to the oxidation of 267 gm. of glucose or 267,000 times the weight of the catalyst. This has been defined as the "calorigenic power" of thyroxin.

One of Boothby's charts, which portrays (1) the effect upon the metabolism of extirpating the thyroid in exophthalmic goiter and (2) the record of the metabolism in myxedema after injecting thyroxin, is given here.

The maximum effect of thyroxin takes place in about 6 days, after which the metabolism gradually declines during 48 days. Perhaps 1 mg. daily may be the necessary quantity of this autacoid.

An interesting discovery is that of Boothby and Sandiford[1] that in exophthalmic goiter the human machine is inefficient in the accomplishment of mechanical work. Twice the number of calories are required to accomplish a given amount of work as are normally needed. It is evident that the patient needs not only increased calories for his basal requirement, but also more for the muscular activities of his life.

Sturgis[2] describes a patient with exophthalmic goiter the basal metabolism of whom was +40 per cent., and he states that the food supply necessary for rest in bed must be 85 per cent. above the normal basal to provide for the almost incessant semi-purposeful movements characteristic of a patient with this disease. This patient with a basal metabolism of +40 per cent., during an attack of tonsillitis with fever, had a metabolism which rose to +104 per cent. of the normal basal level.

The accumulated facts concerning hyperthyroidism lead us to reflect upon the possibility of an analogy between them and the high intake of food by school boys (see pp. 139, 558, 759).

With the possession of such a gland as the thyroid, whose suppression may diminish metabolism 30 per cent. and whose stimulation may increase it 100 per cent., it is truly strange that a normal person should have a basal metabolism so regulated as to correspond to a definite heat loss per square meter of body surface. It is no wonder that the law of surface area should be assailed as incredible and irrational. The real wonder is that the law is true.

[1] Boothby, W. M., and Sandiford, I.: Am. J. Physiol., 1923, **66**, 93.
[2] Sturgis, C. C.: Arch. Int. Med., 1923, **32**, 50.

CHAPTER XXIII

THE PARATHYROIDS AND THE PITUITARY

Is not the Nile very low? . . . You must give my victuals to my people while they are doing work; mind this! . . . Make the most of all my bread. Dig the ground with your noses in the work. Be very active; remember you are eating my bread.—Letter from a father visiting in Lower Egypt to his son living at home in Upper Egypt. Written about B.C. 2001. Found in the tomb of Ipy at Thebes.

THERE is a sharp differentiation between the functions of the thyroid and those of the parathyroid glands.[1] Clonic convulsions are a symptom following parathyroidectomy, and during these periods the temperature rises. MacCallum[2] reports that the temperature of a dog, in which after parathyroidectomy violent tetany developed, rose from 39° to 43.2° during the attack. The administration of calcium acetate stopped the convulsions in a few minutes and within half an hour the temperature fell to 38.9°.

THE PARATHYROID

The original observation of MacCallum and Voegtlin[3] that parathyroid tetany is due to low calcium in the blood has been abundantly confirmed (see p. 509). Greenwald[4] showed that there was an accompanying increase of the inorganic phosphate in the serum.

Binger[5] was able to produce tetany in normal dogs by the intravenous injection of dibasic phosphate. Calcium was thus removed from the circulation and its quantity in the serum fell from 10 mg. to 6 mg., which is the threshold of tetany.

Salvesen[6] kept parathyroidectomized dogs alive for 2 years by giving them milk and calcium chlorid. Dragstedt and Sudan[7] say that the daily administration of 1.8 to 2.4 gm. of calcium lactate per kilogram of body weight to young thyro-parathyroidectomized dogs

[1] For a recent review, Dragstedt, L. R.: Physiol. Reviews, 1927, **7**, 499.
[2] MacCallum, W. G.: "Fever," Harvey Society Lecture, Arch. Int. Med., 1908–09, **2**, 572.
[3] MacCallum, W. G., and Voegtlin, C.: J. Exper. Med., 1909, **11**, 118.
[4] Greenwald, I.: Am. J. Physiol., 1911, **28**, 103.
[5] Binger, C.: J. Pharm. and Exper. Therap., 1917–18, **10**, 105.
[6] Salvesen, H. A.: Proc. Soc. Exper. Biol. and Med., 1922–23, **20**, 204.
[7] Dragstedt, L. R., and Sudan, A. C.: Am. J. Physiol., 1926, **77**, 296.

will prevent tetany and that after 5 to 11 weeks calcium medication is no longer necessary.

It was previously supposed that there was a relationship between alkalosis and tetany, but neither Hastings and Murray[1] nor Greenwald[2] found any disturbance in the acid-base equilibrium.

Collip[3] has prepared from the glands of the ox a potent parathyroid hormone which controls or prevents parathyroid tetany in dogs. This active principle restores the calcium content to the normal level. Overdosage produces hypercalcemia accompanied by anorexia, vomiting, drowsiness verging on coma, and failing circulation which may be fatal in outcome. It increases the calcium in the blood of normal dogs. Greenwald's explanation of the action of the hormone is as follows:

"The parathyroid hormone, or some substance to the preparation of which the parathyroid hormone is essential, maintains calcium in solution in the plasma in excess of the quantities possible in its absence. This hormone, or the substance derived from it or through its participation, is believed to form a component with calcium that somewhat resembles calcium citrate in its general properties. The calcium is in non-ionic, but probably diffusible, form and is in equilibrium with ionic calcium in the solution. The beneficial effects of the various forms of treatment are believed to be due to their effect in increasing the amount of calcium in solution in the blood and other tissues."

Howland and Marriott[4] were the first to call attention to the fact that the calcium content of the blood was low in infantile tetany. Ultra-violet radiation is beneficial here[5] in causing the calcium to rise in the blood.

THE PITUITARY

Abel, Rouiller, and Geiling[6] have separated a principle or hormone, in the form of a tartrate, from the posterior lobe and the pars intermedia of the pituitary body. This principle is present in the aqueous extract of the tissue. Upon smooth muscle the principle

[1] Hastings, A. B., and Murray, H. A., Jr.: J. Biol. Chem., 1921, **46**, 233.

[2] Greenwald, I.: *Ibid.*, 1922, **54**, 285; 1924, **59**, 1; see also Denis, W., and von Meysenbug, L.: *Ibid.*, 1923, **57**, 47.

[3] Collip, J. B.: *Ibid.*, 1925, **63**, 395; Collip, J. B., and Clark, E. P.: *Ibid.*, 1925, **66**, 133.

[4] Howland, J., and Marriott, W. McK.: Quart. J. Med., 1917–18, **11**, 289.

[5] Hoag, L. A.: Am. J. Dis. Child., 1923, **26**, 186.

[6] Abel, J. J., Rouiller, C. A., and Geiling, E. M. K.: J. Phar. and Exper. Therap., 1923, **22**, 289.

is 1000 to 1250 times more stimulating than acid phosphate of histamine. In other words, maximum contraction of the virgin guinea-pig uterus, suspended in Tyrode solution, was secured in a dilution of pituitary tartrate of 1:15,000,000,000. It causes constriction of the blood vessels, increases the contractions of the uterus, and inhibits the secretion of water by the kidney in diabetes insipidus.[1] It behaves exactly like an extract of the gland, and Abel considers it to be the only active principle in the gland.

The result of the extirpation of the pituitary gland in dogs is thus described by Cushing and Goetsch:[2]

"A train of symptoms, coupled with retardation of tissue metabolism and with inactivity of the reproductive glands, not only accompanies states of experimentally induced hypophysial deficiency, but is equally characteristic of clinical states of hypopituitarism. The more notable of these symptoms are a tendency, in the chronic cases, toward an unusual deposition of fat, a lowering of body temperature, slowing of pulse and respiration, fall in blood pressure, and oftentimes a pronounced somnolence."

These results of experimental hypophysectomy were discovered by Cushing[3] in 1909.

Benedict and Homans[4] found that the metabolism of hypophysectomized dogs was lower than the normal. In the young animal Aschner[5] found that the operation caused a great retardation of growth.

The experimental work of Camus and Roussy[6] indicates that the cause of the obesity does not lie in the removal of the pituitary but in damage done to the neighboring tuber cinereum.

Gigantism and acromegaly are the results of *hyperpituitarism.* Evans[7] has fed growing rats with extracts of the anterior lobe and noted that they grow better than the normal controls, becoming gigantic rats, twice as heavy as any known in their stock.

It was Magnus-Levy[8] in 1897 who first showed that in acromegaly the basal metabolism was increased. In an analysis by Cushing and

[1] For literature see Adolph, E. F., and Ericson, G.: Am. J. Physiol., 1926–27, **79,** 377.
[2] Cushing, H., and Goetsch, E.: J. Exper. Med., 1915, **22,** 25.
[3] Crowe, S. J., Cushing, H., and Homans, J.: Johns Hopkins Hosp. Bull., 1910, **21,** 127.
[4] Benedict, F. G., and Homans, J.: J. Med. Research, 1911–12, **25** (N. S. **20**), 409.
[5] Aschner, B.: Pflüger's Arch. gesam. Physiol., 1912, **146,** 1.
[6] Camus, J., and Roussy, G.: J. de physiol. et de path. gén., 1922, **20,** 535.
[7] Evans, H. M.: Harvey Lectures, 1923–24, **19,** 212.
[8] Magnus-Levy, A.: Z. klin. Med., 1897, **33,** 269.

Davidoff[1] it is stated that of 72 cases of acromegaly treated at the Peter Bent Brigham Hospital, 49 had basal metabolisms above the normal (Du Bois standard). These varied from +2 to +61 per cent., the average being +19 per cent. Of the 72 cases, 48.5 per cent. were above +10 per cent. of the normal, whereas in Boothby's series of 30 cases, 50 per cent. were above +10 per cent.

Cushing's hypophysectomies upon 17 acromegalic patients reduced the basal metabolism from an average of +10 per cent. before operation to −7 per cent. after operation.

It is evident that the variation in metabolism from the normal is not so great as in hyperthyroidism.

Means[2] found a diminished metabolism in hypopituitarism with accompanying obesity (*dystrophia adiposogenitalis*). In 107 patients with clinical hypopituitarism Cushing and Davidoff found that the average metabolism was −14 per cent. below the normal level. In 4 cases it was below −30 per cent. Chromophobe adenoma were histologically recognized. In this series 66 per cent. of the cases were lower than −10 per cent. of the normal, and in Boothby's series 54 per cent. fell within this category.

Hypophysectomies performed by Cushing and Davidoff on 24 cases of hypopituitarism, whose basal metabolism was −16 per cent., scarcely changed this figure, the basal metabolism falling only to −18 per cent. The authors conclude,

"Acromegaly is a disease which bears the same relation to pituitary insufficiency (hypopituitarism) that exophthalmic goiter bears to myxedema (hypothyroidism). It is, in other words, an expression of hyperpituitarism just as exophthalmic goiter is of hyperthyroidism."

Hyperthyroidism causes no gross secondary changes in the hypophysis, but acromegaly is commonly associated with a goiter of variable size. However, in 75 per cent. of the cases with definitely elevated metabolism the thyroid was not even palpable.

McKinlay[3] has tested the effect of the subcutaneous administration of extracts of the posterior lobe and pars intermedia of the pituitary upon the basal metabolism under various conditions. The first test of basal metabolism lasted 8 minutes, the pituitary extract was administered within 10 minutes, and the second test was made 12 minutes thereafter. The following results were obtained:

[1] Cushing, H., and Davidoff, L. M.: Arch. Int. Med., 1927, **39**, 673.
[2] Means, J. H.: J. Med. Research, 1915, **32** (N. S. **27**), 121.
[3] McKinlay, C. A.: Arch. Int. Med., 1921, **28**, 703.

Number of Cases		Basal, Per Cent. of Normal	After Pituitary Extract, Per Cent.
5	Normal	− 1	+ 5
4	Hypothyroidism	−15	−17.5
3	Hypopituitarism	−16	− 6

The extract is apparently able to raise the metabolism in hypopituitarism.

A phenomenon which seems passing strange lies in the statement made by Plaut[1] (now Frau Liebeschütz-Plaut) that *in hypopituitarism the specific dynamic action is reduced or abolished.* The basal metabolism was determined and then a breakfast was taken consisting of:

200 gm. minced meat
200 " bread
50 " butter
½ liter coffee

The reaction to this was as follows:

Number of Cases		Per Cent.
39	Basal metabolism (normal controls). Difference from Benedict's prediction	+ 0.2
28	Specific dynamic action (normal controls)	+27.6
24	Basal hypophyseal disease. Difference from Benedict	− 3.4
	Specific dynamic action	+10.6
32	Basal obesity in hypophyseal disease. Difference from Benedict	− 1.9
	Specific dynamic action	+11.6

Plaut found, however, in people who are constitutionally thin, that great increases of +63, +40, and +48 per cent. followed as the result of taking the standard breakfast. The abnormally low rise in constitutional obesity might have been due to a reversal of the conditions which led to the abnormal rise in the condition of thinness.

Kestner, Plaut, and Schadow[2] have also found that, while in dystrophia adiposogenitalis (Fröhlich's syndrome) the metabolism may be increased only 2.5 per cent. by the breakfast, yet on administering aqueous extracts of the anterior lobe for several days the specific dynamic action of the breakfast raises the heat production 17 per cent. The authors therefore conclude that the hypophysis yields a sensitizing substance that the cells may receive the metabolic stimuli of the food-stuffs.

[1] Plaut, R.: Deut. Arch. klin. Med., 1922, **139**, 285; 1923, **142**, 266.
[2] Kestner, O., Liebeschütz-Plaut, R., and Schadow, H.: Klin. Wochenschr., 1926, **5**, 1646.

This work finds striking substantiation in the research of Foster and Smith[1] upon rats. When rats were operated on for total removal of the pituitary, the heat production fell 25 per cent. The administration of glycin now produces no specific dynamic action, as it does in normal controls. The metabolic rate may be restored to normal by the daily injection of anterior lobe extracts, but not by posterior lobe extracts. But extracts of both lobes must be simultaneously injected if the normal specific dynamic action of glycin is to be restored in the hypophysectomized rat.

However recent work by O. H. Gaebler in the Physiological Laboratory of the Cornell Medical College shows that *there is a normal specific dynamic reaction to meat in a hypophysectomized dog.* The operation had been performed by J. E. Sweet, and autopsy revealed a nearly complete removal of the whole gland.

Lublin[2] reports that the ingestion of 38 gm. of glucose by a person suffering from dystrophia adiposogenitalis showed no specific dynamic action either before or after insulin injection. But 38 gm. of glucose is a very small dose.

Reiterating the opinion of Cushing,[3] Davidoff and Cushing[4] conclude from the results of 100 personally observed cases, "Patients with acromegaly (hyperpituitarism) even in the absence of spontaneous glycosuria usually have a low sugar tolerance and tend to show some measure of hyperglycemia, whereas patients with the reverse condition (hypopituitarism) usually have a high tolerance for sugars and ordinarily show a definite hypoglycemia."

Fukui,[5] while confirming the fact that thyroid ingestion causes the liver to lose glycogen, says that extracts of the hypophysis have no influence on the glycogen content of the liver.

Evans, in his Harvey Society Lecture already quoted, concludes that the thyroid is essential for pituitary normality and that pituitary abnormality is the real cause of dwarfism among cretins. A properly functioning anterior hypophysis is essential for adult growth. Also the hypophysis is necessary for the normal functioning of the thyroid, sex gland, and adrenal cortex.

[1] Foster, G. L., and Smith, P. E.: J. Am. Med. Assn., 1926, **87**, 2151.
[2] Lublin, A.: Arch. exper. Path. u. Phar., 1926, **115**, 101.
[3] Cushing, H.: "The Pituitary Body and Its Disorders," Philadelphia and London, 1912.
[4] Davidoff, L. M., and Cushing, H.: Arch. Int. Med., 1927, **39**, 751.
[5] Fukui, T.: Pflüger's Arch. gesam. Physiol., 1925, **210**, 410.

CHAPTER XXIV

METABOLISM IN EXPERIMENTAL DIABETES

In a few years physiology which is already allied with the physical sciences will not be able to advance one particle without their aid. Physiology will acquire the same rigor of method, the same precision of language, and the same exactitude of results as characterize the physical sciences. Medicine, which is nothing more than the physiology of the sick man, will not delay to follow in the same direction and reach the same dignity. Then all those false interpretations which, as food for the weakest minds have so long disfigured medicine, will disappear.—MAGENDIE, in 1836.

IT is said that the sweet taste of diabetic urine was familiar to Susruta, a physician who lived in India during the seventh century. The disease, then as now, may have been more frequent among the Hindoos than elsewhere in the world. In Europe the sweet taste of diabetic urine was discovered by Thomas Willis in 1674, but it was not till after another forty years that Dobson, in 1715, showed that the taste was due to the presence of sugar. Subsequently the coexistence of a hyperglycemia was established.

Claude Bernard found that the stimulation by puncture of a group of cells (the "diabetic center") lying in the medulla near the floor of the fourth ventricle gave rise to an excretion of sugar in the urine. This experiment is the source of the impression that diabetes is essentially of nervous origin. It is called *la piqûre.*

Claude Bernard[1] wrote in 1855:

"It has been thought that every secretion must be directed to an internal or to an external surface and that every secreting organ must be provided with a duct to carry away the products of secretion. The story of the liver now very beautifully establishes the existence of internal secretions, that is to say, secretions whose products are directly transmitted to the blood instead of being carried to the exterior."

Later in 1859 he designated the spleen, thyroid, adrenals, and lymphatic ganglia as being ductless organs of internal secretion. In 1856 Brown-Sequard removed the adrenals and showed that they were essential to life, and in 1859 Shiff extirpated the thyroid in 60

[1] Bernard, C.: "Leçons de physiologie experimentele," Paris, 1855, 1, p. 96.

dogs, but for all that "the idea remained dormant for more than thirty years and the theory remained sterile" (Gley)[1].

In France Lancereaux[2] in 1877, the year of Bernard's death, definitely associated lesions of the pancreas with diabetes. Lépine[3] stated that diabetes was due to the suppression of an internal secretion, and later Laguesse[4] demonstrated that the islets of Langerhans were the responsible organs for the production of the internal secretion. Opie[5] reached the same conclusion as Laguesse.

Diabetes[6] is a disease of particular interest, since it is a departure from the physiologic condition involving the capacity of the organism to care for sugar in the normal fashion. All the symptoms are due to this one fact. No other disease has been more thoroughly investigated. The study of diabetes has wonderfully developed a knowledge of the intermediary metabolism of protein, fat, and carbohydrates. In presenting the details to the reader it may be remarked that the work done is prophetic of possible accomplishment along scientific lines in the study of disease. It is typical of that "scientific medicine" which affrights the spirits devoted to a passing empiricism.

The foundation of modern knowledge on this subject was laid by von Mering and Minkowski[7] and by Minkowski[8] working alone, who extirpated the pancreas in dogs and demonstrated that such animals became diabetic.

Péligot[9] long ago showed that the sugar in diabetic urine was glucose. Geelmuyden[10] analyzed more than 30 diabetic urines which contained much sugar and could not detect the presence of maltose or any of the known disaccharids, though he suspected the presence of monosaccharids other than glucose. Von Noorden[11] states that fructose appears in the urine in cases of severe diabetes.

The causes of the appearance of sugar in the urine are: (1) Either the organism cannot burn sugar, which therefore accumulates in the

[1] Gley, E.: Revue française d'endocrinologie, 1923, **1**, 3.
[2] Lancereaux: Bull. Acad. de Méd., 1877, Ser. 2, **6**, 1215.
[3] Lépine, R.: Lyon médical, 1889, **62**, 620.
[4] Laguesse, E.: Compt. rend. soc. biol. 1893, Ser. 9, **5**, 819; 1894, Ser. 10, **1**, 667; 1895, Ser. 10, **2**, 699.
[5] Opie, E. L.: J. exper. Med., 1900–01, **5**, 397.
[6] For an excellent standard of reference on this subject consult E. P. Joslin's: "The Treatment of Diabetes Mellitus," Philadelphia and New York, 3d ed., 1923.
[7] von Mering, J., and Minkowski, O.: Arch. exp. Path. und Pharm., 1890, **26**, 371.
[8] Minkowski, O.: *Ibid.*, 1892–93, **31**, 85.
[9] Péligot: Compt. rend. de l'Acad. des Sciences, 1838, **7**, 106.
[10] Geelmuyden, H. C.: Z. klin. Med., 1910, **70**, 287.
[11] von Noorden, C.: "Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition," Part 7, "Diabetes," New York, 1905, p. 50.

blood in excess of the normal, and is filtered through the kidney (diabetes mellitus, experimental pancreas diabetes); or (2) some tissues may lose their sugar-retaining function so that the normal regulatory control of the quantity of blood-sugar is lost or diminished as in alimentary glycosuria, phlorhizin glycosuria and possibly in Bernard's piqûre.

The stimulation of Bernard's "diabetic center" is said to be effective in its results only when the liver contains glycogen[1] and that this form of glycosuria cannot be produced in a starving animal. It has been attributed to a sudden flushing of the liver with blood and a conversion of glycogen into sugar, so that hyperglycemia and sugar elimination through the kidney follow.

This interpretation has recently been challenged by the work of Camus, Gournay, and Le Grand,[2] who have been able to produce a glycosuria in rabbits by injury of the tuber cinereum, which persisted in one case for 47 days and at times induced a urinary sugar of 6.4 per cent.

Colwell,[3] in his review of the subject of the relation of the hypophysis to diabetes mellitus, believes that the phenomenon of la piqûre can be fully explained on the basis of a temporary check on the rate of insulin secretion from the islet apparatus of the pancreas and that the tuber cinereum may possibly contain a center which controls this function. He concludes that "it is not impossible that the current conception based on work that is now ancient is in need of revision and that piqûre glycosuria and diabetes are more closely related than has been maintained since the time of Claude Bernard."

Blum[4] was the first to suggest that piqûre influenced the adrenals, causing them to discharge epinephrin, and Trendelenburg[5] finds this to be a sufficient cause of the glycosuria induced. Freund and Marchand[6] find after the extirpation of the adrenals that piqûre causes hyperglycemia, and argue that the adrenals are not the cause.

Ishimori,[7] working under Hofmeister's direction, concluded that although in the fasting rabbit glycogen disappeared in the liver from the periphery of the lobule toward the center without evidence of

[1] Dock, F. W.: Pflüger's Arch. gesam. Physiol., 1872, **5**, 571.
[2] Camus, J., Gournay, J., and Le Grand, A.: Comp. rend. acad. sc., 1923, **77**, 146.
[3] Colwell, A. R.: Med., 1927, **6**, 1.
[4] Blum, F.: Deut. Arch. klin. Med., 1901, **71**, 146.
[5] Trendelenburg, P.: Pflüger's Arch. gesam. Physiol., 1923, **201**, 39.
[6] Freund, H., and Marchand, F.: Arch. exp. Path. und Pharm., 1914, **76**, 324.
[7] Ishimori, K.: Biochem. Z., 1912–13, **48**, 332.

glycogen as such appearing to be discharged, in the case of piqûre, glycogen itself passed from all the cells into the surrounding lymph-spaces and dilated blood-vessels.

Hofmeister[1] has discovered that the fasting organism is more susceptible to alimentary glycosuria than the well-fed one. He calls such a condition "starvation diabetes" (see below).

THE INFLUENCE OF THE LIVER

Macleod[2] found that if the liver were excluded from the circulation by means of an Eck fistula in the dog no hyperglycemia followed asphyxiation. Furthermore, severance of the hepatic nerves did not prevent asphyxial hyperglycemia. Macleod therefore concluded that acids carried in asphyxial blood produced glycogenolysis in the liver cells. Analogous results were obtained by Blum,[3] who found that strychnin convulsions freed a dog's liver of its glycogen even after cutting the vagus and splanchnic nerves. He concluded that chemical coordination was established through the blood between the muscle cells in need of sugar and the liver which could supply it.

Elias[4] found that the intravenous injection of acids into dogs resulted in a discharge of glycogen by the liver, in hyperglycemia and in glycosuria. He suggested that the acidosis in diabetes mellitus might exert a similar influence. In a later paper Elias and Kolb[5] state that the hunger diabetes of Hofmeister is due to the reduced alkalinity of the blood which accompanies fasting. Administration of alkali reduced or prevented this form of glycosuria. Hence, acidosis prevents the normal storage of glycogen.

Kornfeld and Elias[6] in later work find that epinephrin injections which induce glycosuria in rabbits also lower the carbon dioxid combining power of the blood, whereas in man there is only a slight effect and in dogs no effect whatever after similar injections. They therefore suggest that the discharge of glycogen may be due to a local anemia of the liver resulting in the production of acid there.

The acidosis which rapidly develops in both pancreas and phlorhizin glycosuria is, perhaps, the cause of the almost complete removal of glycogen from the liver.

[1] Hofmeister, F.: Arch. exper. Path. u. Pharm., 1889–90, **26**, 355.
[2] Macleod, J. J. R.: Am. J. Physiol., 1908–09, **23**, 278.
[3] Blum, P.: Pflüger's Arch. gesam. Physiol., 1915, **161**, 516.
[4] Elias, H.: Biochem. Z., 1912–13, **48**, 120.
[5] Elias, H., and Kolb, L.: *Ibid.*, **52**, 331.
[6] Kornfeld, F., and Elias, H.: *Ibid.*, 1922, **133**, 192.

Mann and Magath[1] have studied the effect of the total removal of the liver in the diabetic (depancreatized) dog. (1) If the liver and pancreas were removed together the result is the same as though the liver had been removed alone. Hypoglycemia developed with the symptoms already described (see p. 338). (2) When the liver was removed 24 to 96 hours after pancreatectomy the high blood sugar of the diabetic dog fell rapidly, and the same characteristic hypoglycemic symptoms were manifest as in simple hepatectomy, although they developed at a higher blood sugar level. Injection of glucose restored the animal, though the effect was transitory. (3) The total removal of the pancreas and the partial removal of the liver in a dog with an Eck fistula was followed by only a slight or no increase in the blood sugar. The animal lived 10 days without manifesting glycosuria. *These experiments absolutely prove that the presence of the liver is necessary for the hyperglycemia following pancreatectomy.*

In the same year Hendrix and Sweet[2] found that glucose almost vanishes from the urine of a fasting depancreatized dog with an Eck fistula, and these authors suggest that the formation of glucose from amino-acids is greatly diminished in these dogs. This conclusion was verified by Mann later (see p. 211).

Collens, Shelling, and Byron[3] found that in the hyperglycemic stage following the ligation of the hepatic artery the injection of epinephrin did not produce any increase in the blood sugar on account of the lack of glycogen reserves.

Still more striking are the results of Soskin,[4] who removed the intestines, spleen, liver, and pancreas from dogs and found that agents, such as ether, asphyxia, and epinephrin, which ordinarily produce hyperglycemia when administered, now had no effect upon the level of the blood sugar. These results show that the muscles contribute little toward maintaining the level of the blood sugar, but, as Mann and Magath bore witness, this burden falls upon the liver.

It is interesting to recall at this time that Embden's[5] celebrated experiments showed that the perfusion of the liver with leucin, for example, gave rise to large amounts of ketone bodies. However, it appears that these substances may not be oxidized in the

[1] Mann, F. C., and Magath, T. B.: Arch. Int. Med., 1923, **31,** 797.
[2] Hendrix, B. M., and Sweet, J. E.: J. Biol. Chem., 1923, **55,** 161.
[3] Collens, W. S., Shelling, D. H., and Byron, C. S.: Am. J. Physiol., 1927, **79,** 689.
[4] Soskin, S.: *Ibid.*, 1927, **81,** 382.
[5] Embden, G., Salomon, H., and Schmidt, F.: Hofmeister's Beiträge chem. Physiol. u. Path., 1906, **8,** 146.

liver, for Snapper and Grünbaum[1] demonstrate that on perfusing a normal dog's liver with β-hydroxybutyric acid none of it is really oxidized, though a part of it may pass into aceto-acetic acid (see p. 659).

GLYCOGEN CONTENT IN DIABETES

Minkowski[2] noted that the livers of his depancreatized dogs were free from glycogen, and this fact has been confirmed by other observers.

Epstein and Baehr,[3] performed pancreatectomy and double nephrectomy upon a cat which had fasted nine days. The blood-sugar, which before the operation had been 0.06 per cent., rose to 1.1 per cent. forty-eight hours after the operation, at which time the animal was killed. The liver proved to be free of glycogen and the muscle contained only 0.06 per cent. of the substance.

Cruickshank[4] has proved that completely depancreatized dogs do not store glycogen from fructose, as Minkowski affirmed, and this is also noted by Fisher and Lackey.[5] Their enlightening picture of the glycogen condition of normal and depancreatized dogs is shown in the following table:

GLYCOGEN CONTENT OF DOGS

Number of Dogs	Condition	Food Daily per Kg. Body Wt.	Days	Heart	Liver	Muscle
				Per Cent.	Per Cent.	Per Cent.
2	Normal	Fast	5	0.28	0.26	0.09
2	Depancreatized	"	4	0.48	0.07	0.16
3	Depancreatized	"	5	0.18	0.045	0.046
3	Normal	28.7 gm. meat	5	0.50	1.81	0.58
4	Depancreatized	28.7 " "	5–6	0.8	0.11	0.31
1	Normal	28.7 " " + 4.4 gm. glucose	5	0.5	1.52	0.71
1	"	28.7 gm. " + 4.4 " fructose	2	0.46	4.63	0.57
1	Diabetic	28.7 gm. " + 4.4 " glucose	13	1.09	0.045	0.26
1	"	28.7 gm. " + 4.4 " fructose	2	0.52	0.048	0.16
1	"	28.7 gm. " + 4.4 " fructose	4	0.93	0.05	0.28

[1] Snapper, I., and Grünbaum, A.: Biqchem. Z., 1927, **181**, 410.
[2] Minkowski, O.: *Loc. cit.*
[3] Epstein, A. A., and Baehr, G.: J. Biol. Chem., 1916, **24**, 1.
[4] Cruickshank, E. W. H.: J. Physiol., 1913–14, **47**, 1.
[5] Fisher, N. F., and Lackey, R. W.: Am. J. Physiol., 1925, **72**, 43.

In 12 normal dogs the average content of glycogen in the heart muscle was 0.44 per cent. and in 13 diabetic dogs the average was 0.79 per cent. *Partially* depancreatized dogs may store glycogen; wholly depancreatized dogs treated with insulin and fed with carbohydrate give nearly normal glycogen values.[1]

Beattie and Milroy,[2] from their experiments on the adductor muscles of normal and depancreatized cats, conclude that the carbohydrate mechanism is a very stable one and that resistance is offered to the depletion of the glycogen store. Thus normal well fed animals, after fasting 2 days, contain 0.5 per cent. muscle glycogen, and the depancreatized 0.6 to 0.12 per cent. In the latter group, in the lethargic stage 4 days after pancreatectomy, the original glycogen content of the muscles may be found.

This is the reason why depancreatized dogs retain their capacity of forming lactic acid during strychnin convulsions or running. As long as the muscles contain glycogen, lactic acid (see Barr, p. 443) is formed during contractions.[3]

The behavior of the glycogen reserves in phlorhizin glycosuria has already been discussed (see p. 444).

In the theoretical consideration of diabetes much has been made of the influence of epinephrin upon the metabolism of carbohydrate. This will be described more fully later, but it may be of interest to allude here to this influence and to give the results found by Junkersdorf,[4] a past master in the art of glycogen determinations done by the method which he learned directly from Pflüger himself. Epinephrin was administered to 4 fasting dogs once daily. Aside from motor disquiet and forced respiration immediately after giving the substance the animals appeared to be normal. The blood withdrawn for sugar determination was taken 3 hours after the injection of epinephrin.

If one contrasts these glycogen values with those of the normal fasting dogs of Fisher and Lackey it appears that both the liver and muscle glycogen are slightly less in quantity and that the heart, as in diabetes, has protected itself by increasing its supply.

[1] Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.: Trans. Roy. Soc. Canada, 1922, Sec. V, **16**, 39.

[2] Beattie, F., and Milroy, T. H.: J. Physiol., 1926–27, **62**, 174.

[3] Doisy, E. A., Briggs, A. P., Weber, C. H., and Koechig, I.: J. Biol. Chem., 1925, **63**, p. xlviii; Weber, C. H., Briggs, A. P., and Doisy, E. A.: *Ibid.*, **66**, 653.

[4] Junkersdorf, P., and Török, P.: Pflüger's Arch. gesam. Physiol., 1926, **211**, 414.

ACTION OF EPINEPHRIN IN FASTING

Dog Number		Epinephrin	Urine N	Blood Sugar	Glycogen in Per Cent.			Liver Fat
					Liver	Heart	Muscle	
			Gm.	Per Cent.				Per Cent.
I	6th day fast	..	4.55	0.097				
	7th " "	+	4.74	0.189				
	8th " "	+	5.60	0.084				
	9th " "	+	4.75	0.074	0.09	0.86	0.02	27
II	6th " "	..	3.72	0.084				
	7th " "	+	....	0.184				
	8th " "	+	4.68	0.102				
	9th " "	+	4.45	0.156	0.12	0.57	0.11	29
III	Similar treatment	..	....	.....	0.05	0.66	0.11	22
IV	" "	..	....	.....	0.16	0.54	0.01	18
	Average.....	..	....	.....	0.11	0.66	0.06	24

The blood sugar rises after the first injection of epinephrin, a phenomenon which Junkersdorf attributes to the production of sugar from fat. It is difficult to follow this reasoning because on the 2d day of epinephrin administration no increase in the blood sugar takes place. It would seem that the rise on the first day was due to glycogenolysis. When on the 2d day there was no longer an available source of glycogen subject to draft, no increase in blood sugar took place.

THE BLOOD SUGAR

S. R. Benedict[1] writes as follows:

"The more we have hunted for the elusive 'glucose threshold,' the more we feel that this is quite possibly wholly an artifact. We tend to adopt the view that the causes leading to glucose excretion by the kidney are usually the same as those leading to an increase in the blood sugar, but we question that the two latter phenomena need be always causally related. The low 'threshold' at which glucose appears in the urine in large amounts in some cases of early diabetes, and the persistence of high blood sugar after cessation of glycosuria in diabetes would be in accord with our view."

Benedict, Osterberg, and Neuwirth[2] have shown that 1.5 gm. of urinary sugar may be eliminated normally per day. Taussig[3] reports

[1] Benedict, S. R., and Osterberg, E.: J. Biol. Chem., 1923, **55**, 769.
[2] Benedict, S. R., Osterberg, E., and Neuwirth, I.: *Ibid.*, 1918, **34**, 217.
[3] Taussig, A. E.: Med. Clinics North America, 1924, **7**, 1545.

a case of a boy who had been rejected for life insurance, who passed 2.5 gm. of glucose in the urine daily irrespective of the diet administered and with a blood sugar varying between 0.07 and 0.085. This he calls "innocent" diabetes.

No general discussion of the blood sugar in diabetes can here be attempted, but perhaps the results obtained lately by Rabinowitch,[1] who compared the blood sugar before and after injecting 25 gm. of glucose into normal and severely diabetic persons, may be of interest:

	Number of Persons		Sugar in Per Cent.	
			Arterial Blood	Venous Blood
Normal	6	Fasting	0.092	0.089
"	6	30 min. after 25 gm. glucose	0.218	0.165
Severe diabetes	5	Fasting	0.231	0.236
" "	5	30 min. after 25 gm. glucose	0.346	0.349
Diabetic coma	3	Fasting	0.509	0.527

In the normal condition the tissues may retain glucose. In the diabetic condition this is not readily done. In the fasting diabetic in coma the tissues were evidently feeding glucose into the venous blood stream. The diabetic acidosis would tend to convert the residual glycogen into glucose.

Lennox[2] has injected intravenously about 100 gm. of glucose into a normal man at the rate of 3 gm. per minute for 35 minutes and has witnessed the blood sugar rise to 0.505 per cent. It then fell readily thereafter to a level of 0.05 per cent., at which point mild hypoglycemic reactions were manifest. The interpretation placed on these results is that an overstimulation of insulin production resulting from the hyperglycemia led to hypoglycemia.

PSYCHIC GLYCOSURIA

Böhm and Hoffmann[3] report that a dog barking at a cat induces glycosuria in the cat. Cannon and co-workers[4] term this "emotional glycosuria," and have found that the cat's blood contains an increased quantity of epinephrin as a sequence to the fright. This

[1] Rabinowitch, I. M.: British J. Exper. Path., 1927, **8**, 76.
[2] Lennox, W. G.: J. Biol. Chem., 1927, **73**, 237.
[3] Böhm, R., and Hoffmann, F. A.: Arch. exp. Path. und Pharm., 1878, **8**, 280.
[4] Cannon, W. B., Shohl, A. T., and Wright, W. S.: Am. J. Physiol., 1911–12, **29**, 280.

increased amount of epinephrin becomes the exciting cause of dilatation of the pupil, inhibition of the movements of stomach and intestines, acceleration of the heart, erection of the hairs on the back and on the tail, and the discharge of glycogen.

In controversy with G. N. Stewart, Cannon and Britton[1] deny that the mechanism at work during a barking dog *versus* cat episode is a "myth," as Stewart describes it. An angered or frightened cat, with denervated heart, liver, and thyroid, responds with an accelerated heart beat because epinephrin is liberated from the adrenal, and the cat, after resting quietly on a soft cushion, does not recover from excitement for 20 minutes. Rest is required after anger or fright.

Cannon has elaborated these results and presented them in the form of a popular book which holds that emotional impulses act upon the adrenals, causing them to discharge epinephrin, which, in turn, mobilizes the physical and chemical resources of the body for supreme mechanical effort in both attack and defense. He believes that this mechanism collaborates with the nerve impulses in practically all the activities which are aroused in excitement, asphyxia, or cold. (See p. 159.)

Tying down a frightened rabbit to a board results in psychic glycosuria, the blood-sugar rising to 0.4 or 0.5 per cent. and the urine containing as high as 7.8 per cent. of sugar.[2]

The urines of 34 men and of 36 women students were tested by Folin[3] before and after college examinations: 6 men and 6 women showed small but unmistakable traces of glycosuria immediately after examination. This further illustrates the phenomenon of emotional glycosuria.

It is reported from Finland[4] that, of students taking examinations, 7 of 10, or 70 per cent., who were in the *cum laude* class, manifested glycosuria, whereas of those who were not adjudged worthy of this honor 29 per cent. only had glycosuria. The most marked results were produced by an examination in mathematics, but when the examination was in the Finnish language, the mother tongue, only one pupil showed sugar in the urine.

[1] Cannon, W. B., and Britton, S. W.: Am. J. Physiol., 1926–27, **79**, 433.
[2] Hirsch, E., and Reinbach, H.: Z. physiol. Chem., 1913, **87**, 122.
[3] Folin, O., Denis, W., and Smillie, W. G.: J. Biol. Chem., 1914, **17**, 519.
[4] Malmiwirta, F., and Mikkonen, H.: Skan. Arch. Physiol., 1924, **45**, 68.

Moritz[1] observed 0.2 to 0.3 per cent. of sugar in the urine of 4 out of 6 healthy people who had partaken of a quantity of sweets and champagne.

Evidently such conditions as these are not to be classed with diabetes mellitus, where there is a fundamental disturbance in the sugar-burning power in the organism. It would be of service to distinguish between glycosurias where the *sugar-holding* capacity of the organs has been diminished or overstrained, and the glycosuria of *diabetes* in which the *sugar-burning* capacity has been affected. For example, Kleiner and Meltzer[2] injected intravenously 4 grams of glucose per kilogram of animal into both normal and depancreatized dogs. The blood-sugar rose greatly in both groups of animals, but in the normal animals there was a rapid readjustment through elimination by the kidney, glycogen retention, and oxidation of glucose, whereas in the depancreatized animals, though removal of the glucose by the kidney was active, the other two functions were in abeyance and the blood-sugar continued at a high level long after it had readjusted itself in the normal animals.

PHLORHIZIN GLYCOSURIA[3]

A special type of glycosuria is caused by phlorhizin injections, as was discovered by von Mering,[4] who found that the injection into a dog of 0.05 gm. of the substance would cause the elimination of 8.8 gms. of glucose in the urine in 8 hours. Here the blood itself while passing through the kidney loses the power of retaining its normal sugar content and a hypoglycemia results. Sometimes when the kidney is altered in Bright's disease phlorhizin is ineffective and no glycosuria follows its administration. The renal character of phlorhizin glycosuria was demonstrated by Zuntz,[5] who placed cannulæ in the upper portions of the two kidneys and injected phlorhizin into the renal artery of one. On the injected side sugar-containing urine appeared in two minutes, and three minutes later the kidney on the opposite side yielded sugar through its ureter. The delay was due to the lapse of time necessary for the transportation of the phlorhizin

[1] Moritz, F.: Deut. Arch. klin. Med., 1890, **46**, 217.

[2] Kleiner, I. S., and Meltzer, S. J.: Am. J. Physiol., 1914–15, **36**, 361.

[3] A complete review of this subject prior to 1912, Lusk, G.: Ergeb. d. Physiol., 1912, **12**, 315; subsequent to 1912, Nash, T. P., Jr.: Physiol. Reviews, 1927, **7**, 385. See also Cremer, M. and Seuffert, R. W.: Handb. d. exp. Pharmak., 1924, **2**, Part 2, 1453.

[4] von Mering, J.: Verhandlungen des 5ten Congresses für innere Medizin, 1886, p. 185.

[5] Zuntz, N.: Arch. f. Physiol., 1895, p. 570.

by the blood-stream from the injected kidney to the other one. In this form of glycosuria sugar ingested *per os*, or subcutaneously, or as formed in protein metabolism, may be eliminated in the urine.[1]

Minkowski found that, although after nephrectomy in the depancreatized dog the blood sugar rose from 0.3 to 0.6 per cent. in 5 hours, the administration of phlorhizin to a nephrectomized dog caused no immediate change in the level of the blood sugar. Recently Deuel, Wilson, and Milhorat[2] have confirmed this and have proved that the respiratory quotients obtained from nephrectomized-phlorhizinized dogs, both in fasting and after carbohydrate ingestion, are similar to those obtained upon normal dogs.

Nash[3] found that in phlorhizinized dogs the blood of the renal vein contains less sugar than does the general arterial blood. This confirms the idea of the existence of an increased renal permeability.

De Boer and Verney[4] have added glucose and phlorhizin to the blood in one of Starling's heart-kidney-lung preparations. The sugar was eliminated by the kidney until it was all removed from the blood. Roughly, the extra sugar disappearing from the blood (after deducting the amount used by the circulating scheme itself) corresponded to the amount eliminated in the urine. Hartwich[5] has perfused the isolated frog's kidney and finds a glycosuric action when phlorhizin is in a concentration of 1:1,000,000. Between 1:50,000 and 1:5000 there is a high secretion, but in concentrations of 1:3000 the secretory activity is lowered.

Phlorhizin glycosuria is only temporary in character and subcutaneous injections of 1 gm. in 25 c.c. of a 1.2 per cent. sodium bicarbonate solution three or four times daily may be necessary to obtain constant results. A more convenient method is that of Coolen,[6] who noticed that the subcutaneous injection of 1 gm. of phlorhizin, suspended in 7 c.c. of olive oil, caused a glycosuria of maximal intensity which lasted for between 5 and 10 days. Loewi[7] administered 6 mg. in oil to a dog and obtained 6.6 gm. of glucose in 600 c.c. of urine. The necessary dose required for maintaining maximal phlorhizin glycosuria has never been determined, but common

[1] Stiles, P. G., and Lusk, G.: Am. J. Physiol., 1903–04, **10**, 67.
[2] Deuel, H. J., Jr., Wilson, H. E. C., and Milhorat, A. T.: J. Biol. Chem., 1927, **74**, 265.
[3] Nash, T. P., Jr.: *Ibid.*, 1922, **51**, 171.
[4] de Boer, S., and Verney, E. B.: J. Physiol., 1923–24, **58**, 433.
[5] Hartwich, A.: Arch. exper. Path. u. Pharm., 1926, **115**, 328.
[6] Coolen, F.: Arch. de pharmacodynamie, 1895, **1**, 267.
[7] Loewi, O.: Arch. exper. Path. u. Pharm., 1902, **47**, 48.

laboratory practice calls for the injection of a gram daily in oil. Much less may be necessary. In order to be certain of a maximal effect Deuel, Wilson, and Milhorat administered 1 gm. of phlorhizin in oil and 1 gm. in alkali, both subcutaneously.

In our laboratory 100 gm. of Merck's commercial phlorhizin is always recrystallized from solution in 1000 c.c. of 95 per cent. alcohol by adding 3000 c.c. of water and leaving in the ice box for several days. About 88 gm. are recovered. The original substance often induces unwanted convulsions, a phenomenon not noticed of the material furnished 30 years ago.

Extirpation of the spleen has no influence upon the course of phlorhizin glycosuria.[1] Nor has the establishment of an Eck fistula.[2] An Eck fistula is one which diverts the whole of the portal circulation to the liver into the inferior vena cava, and leaves the liver supplied by the hepatic artery only.

Levene found that the bile contained a small amount of glucose after the administration of phlorhizin, and this has been confirmed by Woodyatt.[3] Adelsberger and Róth[4] state that in the rabbit phlorhizin may cause simultaneous production of a urine containing 6.7 per cent. of sugar or 1.5 gm. and bile containing 0.5 per cent. or 0.03 gm. At times the authors could find no sugar in the bile.

Loewi[5] has conceived the idea that the blood-sugar is normally in a loose combination with colloid substance. This colloid sugar cannot pass through the glomerulus. If, however, sugar accumulates in the blood above the combining power of the colloid, then the crystalloid glucose readily passes away through the kidney. This condition exists in diabetes mellitus. In phlorhizin glycosuria the kidneys break up the colloid sugar, and the sugar may then be eliminated. Stiles and Lusk, while accepting Loewi's theory, have added the hypothesis that colloid sugar cannot be burned. Phlorhizin acting in the kidney will split the compound and permit the elimination of sugar. Any free glucose in the general circulation unites with the colloid radicle and is protected from combustion, as is the case when 5 grams of glucose are administered subcutaneously, only to reappear in the urine (Stiles and Lusk). The presence of a colloid-glucose combination is denied by Rosenfeld and Asher,[6] who

[1] Austin, J. H., and Ringer, A. I.: J. Biol. Chem., 1913, **14**, 139.
[2] Sweet, J. E., and Ringer, A. I.: *Ibid.*, p. 135.
[3] Woodyatt, R. T.: *Ibid.*, 1909–10, **7**, 133.
[4] Adelsberger, D., and Róth, E.: Arch. exper. Path. u. Pharm., 1927, **121**, 131.
[5] Loewi, O.: *Ibid.*, 1902, **48**, 410.
[6] Rosenfeld, R., and Asher, L.: Zentralbl. f. Physiol., 1905, **19**, 449.

find that the sugar of normal blood is readily diffusible. Kleiner,[1] however, states that in depancreatized dogs a mechanism exists which tends to hinder the dialysis of blood sugar, and he believes it possible that a "combined sugar" exists in diabetic blood. John[2] states that there is no colloid-glucose combination; it is an "obsolete idea."

Is Phlorhizin Diabetes a Complete Diabetes?—This is an old question. The injection of phlorhizin into a dog does not at first affect the respiratory quotient (see p. 637). Later, after the dog has fasted 2 or 3 days, when the D:N ratio is found to be 3.65:1 the respiratory quotient is 0.69, which accords with the theory. In rare cases persistent ratios as high as 4.4 have been observed. The ratio may often occur at the level of 2.8, especially when unpurified phlorhizin is used. At both the ordinary levels, 3.65 and 2.8, one finds that ingested glucose is nearly completely recovered as extra sugar in the urine if the method of calculation given on page 228 is employed. Thus, Reilly, Nolan, and Lusk gave 24 gm. of glucose to a large dog and recovered 22.5 gm. or 94 per cent. as extra glucose in the urine. Ringer[3] gave 75 gm. in six doses to a phlorhizinized dog and recovered 69.5 gm. or 93 per cent.

Ringer and Lusk[4] gave 20 gm. of i-alanin and recovered 18.76 and 18.78 gm. as extra sugar. Since 20 gm. of alanin after deamination are convertible into 20.22 gm. of glucose, the recovery was 93 per cent. and it was concluded that i-alanin was completely convertible into glucose. Results of this completeness were not obtained by Csonka[5] with alanin, though ingested glucose was completely eliminated. In Ringer and Lusk's experiments after giving 20 gm. of glycin, which is theoretically convertible into 16 gm. of glucose, recoveries of 12.2, 14.8, 13.3, 11.1, and 15.8 were obtained. But the authors accepted the higher yields as the true values and believed that both carbon atoms of glycin were convertible into glucose.

Nash and Benedict[6] found that of 30 gm. of glucose ingested by a phlorhizinized dog 95.5 per cent. was recovered as extra sugar in the urine of the subsequent 24 hours. The blood sugar rose from 86 mg. per 100 c.c. to 242 mg. In another case 86 per cent. of the sugar

[1] Kleiner, I. S.: J. Biol. Chem., 1918, **34**, 471.
[2] John, H. J.: Arch. Int. Med., 1923, **31**, 555.
[3] Ringer, A. I.: J. Biol. Chem., 1912, **12**, 431.
[4] Ringer, A. I., and Lusk, G.: Z. physiol. Chem., 1910, **66**, 106.
[5] Csonka, F. A.: J. Biol. Chem., 1915, **20**, 539.
[6] Nash, T. P., Jr., and Benedict, S. R.: *Ibid.*, 1923, **55**, 757.

ingested was recovered as extra glucose. The authors conclude that phlorhizin produces a distinct impairment of the sugar oxidizing mechanism.

Sansum and Woodyatt[1] could recover only 86 to 75 per cent. of 16 gm. administered. Wierzuchowski[2] recovered 90 and 94 per cent. of the glucose given to one dog, 95 per cent. in another, whereas recoveries in seven additional experiments varied between 71 and 84 per cent. The average of ten experiments showed recoveries of only 82 per cent. Wierzuchowski was the first to show that a small amount of glucose may be oxidized (see p. 634).

Lusk,[3] after giving 10 gm. of glucose or 10 gm. of fructose to the completely phlorhizinized dog was unable to find any rise in the respiratory quotient which would indicate their oxidation.

In a careful series of experiments upon phlorhizinized dogs which were placed in the respiration calorimeter immediately after giving 16 gm. of glucose the following results were obtained by Deuel, Wilson, and Milhorat:[4]

RECOVERY OF GLUCOSE INGESTED IN PHLORHIZIN DIABETES

Dog Number	Extra Urinary Glucose	Glucose Oxidized	Calculated Recovery
	Gm.	Gm.	Gm.
1	12.7	3.3	16.0
1	14.4	2.6	17.0
1	14.6	3.7	18.3
2	15.3	4.1	19.4
2	15.9	1.9	17.7
Average	14.6	3.1	17.7
In per cent.	91	20	111

There was an invariable rise in the respiratory quotients of the second, third, and sometimes the fourth hours after giving 16 and 10, but not after giving 5 gm. of glucose. The calculated average recovery of 16 gm. of glucose is 91 per cent., which on the whole is the best one has a right to expect of a method into which so many complicated factors enter. It is clear that a small and variable amount of glucose undergoes oxidation, though this factor may be exaggerated in the results calculated. In the third edition of this book it was stated, and

[1] Sansum, W. D., and Woodyatt, R. T.: J. Biol. Chem., 1916, **24**, 23.
[2] Wierzuchowski, M.: *Ibid.*, 1927, **73**, 445.
[3] Lusk, G.: *Ibid.*, 1915, **20**, 555.
[4] Deuel, H. J., Jr., Wilson, H. E. C., and Milhorat, A. T.: *Ibid.*, 1927, **74**, 265.

in this edition it is restated on p. 250 that the analytic method is admittedly crude.

An interesting comparison of the analysis of the carbohydrate content of cabbage and of cauliflower by the takadiastase method and by the means of the phlorhizinized dog has been accomplished by Olmstead.[1]

Substance Analyzed	Available Carbohydrate	
	Takadiastase Method	Phlorhizin Dog Method
	Per Cent.	Per Cent.
Cabbage	4.4	5.0
Cabbage, thrice boiled	0.4	0.5
Cauliflower	2.8	3.4
Cauliflower, thrice boiled	0.8	0.8
Spinach	...	1.2

The Influence of Insulin in Phlorhizin Diabetes.—Richardson and Shorr[2] have investigated the capacity to oxidize carbohydrate by the excised surviving tissue of kidney or testes of the phlorhizinized rat, using the method developed by Warburg for the study of the respiratory exchange *in vitro*. In all cases such tissue was freely able to oxidize added carbohydrate, as was indicated by an increase of the respiratory quotient.

Nash and Benedict,[3] as well as Cori,[4] have discovered that ample supplies of insulin are present in the pancreas, liver, muscle, and blood of the completely phlorhizinized dog.

Investigations by M. Ringer[5] on the influence of insulin injections upon a dog with phlorhizin diabetes were made under conditions now known to result in the oxidation of small amounts of glucose even without the addition of insulin. Cori[6] states that administration of insulin to phlorhizinized rabbits (1) reduces the blood sugar, (2) increases the glycogen in the liver, and (3) decreases the D:N ratio. The day after insulin injection the D:N ratio rises and the liver glycogen falls.

In experiments by Nash[7] it was found that, whereas 91 per cent. of ingested glucose was recovered in phlorhizin diabetes, only 72 per

[1] Olmstead, W. H.: J. Biol. Chem., 1920, **41**, 45.
[2] Richardson, H. B., and Shorr, E.: J. Clin. Invest., 1927, **4**, 438.
[3] Nash, T. P., Jr., and Benedict, S. R.: J. Biol. Chem., 1924, **61**, 423.
[4] Cori, G. T.: Am. J. Physiol., 1924–25, **71**, 708.
[5] Ringer, M.: J. Biol. Chem., 1923–24, **58**, 483.
[6] Cori, C. F.: Proc. Soc. Exper. Biol. and Med., 1923–24, **21**, 417.
[7] Nash, T. P., Jr.: J. Biol. Chem., 1925, **66**, 869.

cent. was obtainable if 40 gm. of glucose and 40 units of insulin were given together in this condition, and also he reported that insulin favored the deposition of glycogen in the livers of such dogs.

It is probable that insulin merely fulfills its physiological function under these circumstances (see p. 324). Colwell,[1] however, believes that it also exerts a toxic action on the kidney.

PANCREAS DIABETES

Von Mering and Minkowski[2] removed the pancreas from dogs and obtained a condition which was markedly analogous to diabetes mellitus in man. There is hyperglycemia and a large excretion of glucose in the urine; ingested glucose cannot be burned, but is completely eliminated. The dogs show a considerable acidosis with excretion of β-oxybutyric acid, and they die in coma.[3] If a portion of the gland remain in the abdominal cavity there is either no diabetes or only a partial diabetes. Minkowski[4] reports that if a piece of the pancreas be ingrafted under the skin of a dog and afterward the whole of the remainder of the pancreas be removed from the abdomen, the dog's urine remains free from sugar for two months, but on extirpation of the piece ingrafted under the skin an extreme diabetes sets in.

Allen[5] states that a dog which has a large part of its pancreas removed, but is free from diabetes, may gradually become diabetic by giving protein and fat, and may then manifest the spontaneous downward progress observed in human patients. Jensen and Carlson[6] make the following somewhat non-committal statement:

"In general, our results support the view that a liberal carbohydrate diet tends to change diabetes *levis* into diabetes *gravis*, after partial pancreatectomy in dogs. But our experiments do not constitute a clear demonstration of this thesis, in fact they are not much more conclusive than the experiments reported earlier by Thirolaix,[7] and by Allen."

[1] Colwell, A. R.: J. Biol. Chem., 1924, **61,** 289.
[2] von Mering, J., and Minkowski, O.: Arch. exp. Path. und Pharm., 1889–1890, **26,** 371.
[3] Allard, E.: *Ibid.*, 1908, **59,** 391.
[4] Minkowski, O.: *Ibid.*, 1908, Suppl., p. 399.
[5] Allen, F. M.: "Harvey Lectures," Philadelphia and London, 1916–17, p. 42.
[6] Jensen, V. W., and Carlson, A. J.: Am. J. Physiol., 1920, **51,** 423.
[7] Thirolaix, J., and Jacob: Compt. rend. acad. sc., 1912, **154,** 377.

By an operation which united the blood supply of two dogs Forschbach[1] established the condition of parabiosis. On the removal of the pancreas from one of the dogs neither developed diabetes. An analogous experiment is that of Carlson,[2] who performed pancreatectomy upon bitches near to term and found little or no sugar in the urine. Here the embryo apparently furnished the mother with the substance essential to sugar oxidation. Murlin, however, in unpublished experiments finds that such dogs have diabetic respiratory quotients (0.69), and suggests that the absence of glucose from the urine is due to carbohydrate retention by the fetus. Markowitz and Soskin[3] also observed that pregnant diabetic dogs were unable to oxidize glucose.

Remarkable experiments are reported by La Barre[4] in which the superior pancreatic vein of a large dog was joined to the jugular vein of a smaller depancreatized dog. The hyperglycemia of the recipient was reduced. Stimulation of the right vagus nerve of the donor provoked a hypersecretion of insulin as manifested by a more rapid fall in the blood sugar of the recipient.

THE DEXTROSE: NITROGEN (D:N) RATIO

It has long been known that diabetics eliminate sugar even after all administration of sugar is stopped. It has also been generally recognized that protein ingestion tends to increase the sugar output in the urine, while fat has no effect.

A large amount of information has been collected concerning the relation between the urinary nitrogen and sugar elimination in the fasting and meat-fed diabetic organism. The dextrose to nitrogen ratio (D:N) is a key to the problem of the quantity of sugar which can be derived from protein metabolism (p. 207).

Minkowski[5] was the pioneer who discovered that depancreatized dogs, whether fasting or fed with meat, showed a constant elimination of 2.8 grams of glucose for each gram of nitrogen in the urine. This ratio (D:N::2.8:1) was the average obtained from 7 dogs on twenty-two different days. The lowest ratio was 2.62:1, the highest 3.05:1. Some other operators have been unable to obtain these ratios.

[1] Forschbach, J.: Arch. exp. Path. und Pharm., 1909, **60,** 131.
[2] Carlson, A. J., Orr, J. S., and Jones, W. S.: J. Biol. Chem., 1914, **17,** 19.
[3] Markowitz, J., and Soskin, S.: Am. J. Physiol., 1927, **79,** 553.
[4] La Barre, J.: Arch. inter. physiol., 1927, **29,** 227, 238.
[5] Minkowski, O.: Arch. exp. Path. und Pharm., 1893, **31,** 85, 97.

Pflüger[1] finds a variable and generally lower ratio, and his dogs all died of abscesses. Embden's[2] ratios are all lower than Minkowski's, and are due to incomplete extirpation of the pancreas.

The accuracy of Minkowski's results is indicated by the fact that the ratio (D:N::2.8:1) may be easily established by the administration of phlorhizin to rabbits, goats, cats, and in certain dogs whose kidneys have been somewhat affected, as, for example, by giving camphor. Phlorhizin acts first to cause a sweeping out of the excess of sugar in the organism, with a subsequent establishment of the ratio. (See table, p. 634.) The ratios in different animals are given in the following table:

RATIOS IN DIABETES OF D:N::2.8:1

Day	Dog[3]	Dog[4]	Cat[5]	Goat[6]	Rabbit[7]
	Pancreas Diabetes	Phlorhizin and Camphor	Phlorhizin	Phlorhizin	Phlorhizin
Second day of diabetes...	....	...	....	2.95	2.89
Third day of diabetes....	2.88	...	2.93	2.90	2.69
Fourth day of diabetes...	2.94	...	2.80	2.78	
Fifth day of diabetes.....	3.09	...	2.93		
Day unknown.....	....	2.8			

The uniformity of the ratio as shown in different animals is very striking. One may calculate from these results that 45 per cent. of the protein molecule may be converted into dextrose in the course of metabolism.

This, however, does not complete the story of the D:N ratio, for a higher ratio, or 3.75:1, was discovered by Reilly, Nolan, and Lusk[8] in the urine of dogs with normal kidneys, after subcutaneous injections of phlorhizin. This ratio was subsequently revised by Stiles and Lusk[9] and found to be 3.65:1. The importance of this discovery was enhanced by the finding of Mandel and Lusk[10] that the same ratio

[1] Pflüger, E. F. W.: "Das Glycogen," Bonn, 2d ed., 1905, p. 491.
[2] Embden, G., and Salomon, H.: Hofmeister's Beitr. chem. Physiol. u. Path., 1905, **6**, 63.
[3] Minkowski, O.: *Loc. cit.*, p. 97.
[4] Jackson, H. C.: Am. J. Physiol., 1902–03, **8**, p. xxxii.
[5] Arteaga, J. F.: *Ibid.*, 1901–02, **6**, 175.
[6] Lusk, G.: Z. f. Biol., 1901, **42**, 43.
[7] Reilly, F. H., Nolan, F. W., and Lusk, G.: Am. J. Physiol., 1898, **1**, 396.
[8] Reilly, F. H., Nolan, F. W., and Lusk, G.: *Ibid.*
[9] Stiles, P. G., and Lusk, G.: *Ibid.*, 1903, **10**, 67.
[10] Mandel, A. R., and Lusk, G.: Deut. Arch. klin. Med., 1904, **81**, 479.

may exist in human diabetes when the patient is given a diet of meat and fat. The ratios found on successive days are thus comparable:

Phlorhizinized Dog	Phlorhizinized Man	Diabetes Mellitus in Man			
3.60[1]	3.58[2]	3.60[3]	3.75[4]	3.41[5]	3.39[5]
3.65	3.82	3.65	3.56	3.76	3.68
3.66	3.66	3.66	3.70	3.98	3.62
3.62	....	....	....	3.78	3.84
3.63	3.68	3.64	3.66	3.73	3.63

In another place (p. 208) it has been shown that the D:N ratio does not vary after the ingestion of sufficient meat to double the quantity of nitrogen in the urine; the sugar also doubles. The sugar production is therefore proportional to the protein metabolism, and, apparently, must be derived from protein.

Various objections have been raised to this statement. Other experiments, however, confirm the above proposition.

Lüthje[6] gave "nutrose" to a depancreatized dog. "Nutrose" contains casein, but no sugar. The dog weighed 5.8 kilograms and eliminated 1176 grams of glucose during twenty-five days. The tissues of the dog could not possibly have contained over 232 grams of glycogen at the beginning of the experiment. The source of the sugar could not have been the animal's store of glycogen, but it must have arisen from either protein or fat.

There appear from time to time descriptions of work purporting to have been done upon completely depancreatized dogs which seem to indicate that the surgical performance of pancreatectomy is a lost art. That the art still survives is apparent from the work of von Falkenhausen,[7] of the Breslau Poliklinik, done under the shadow of the great master, Minkowski. These results have been tabulated and contrasted with those found in phlorhizin diabetes.

On analysis this table shows the following average relationships:

Pancreas diabetes, 3d to 10th day, 87.1 gm. D: 30.1 gm. N:: 2.89:: 1.
Phlorhizin diabetes, 3d to 11th day, 551.5 gm. D: 147.8 gm. N:: 3.73:: 1.

[1] Stiles, P. G., and Lusk, G.: *Loc. cit.*, p. 77. (Details, this book, p. 106.)
[2] Benedict, S. R., and Lewis, R. C.: Proc. Soc. Exper. Biol. and Med., 1914, **11**, 134. (Details unpublished.)
[3] Mandel, A. R., and Lusk, G.: *Loc. cit.*, p. 479.
[4] Greenwald, I.: J. Biol. Chem., 1913–14, **16**, 375.
[5] Wilder, R. M., Boothby, W. M., and Beeler, C.: *Ibid.*, 1922, **51**, 311.
[6] Lüthje, H.: Pflüger's Arch. gesam. Physiol., 1905, **106**, 160.
[7] von Falkenhausen, M.: Arch. exper. Path. u. Pharm., 1925, **109**, 249.

COMPARISON BETWEEN THE D:N RATIOS OF A FASTING DEPANCREATIZED DOG (VON FALKENHAUSEN, 1925) AND A FASTING AND MEAT-FED PHLORHIZINIZED DOG (REILLY, NOLAN, AND LUSK, 1898)

Day of Diabetes	Pancreas Diabetes Weight = 7.5 Kg.				Phlorhizin Diabetes Weight = 21.4 Kg.				
	Day of Fast	Urine			Day of Fast	Urine			Food Every 8 Hrs.
		N	D	D:N		N	D	D:N	
		Gm.	Gm.			Gm.	Gm.		
	4	1.76							
	5	1.80			1	4.04			
	6	1.68			2	4.17			
1	7	*			3	12.66‡	63.6	5.02	
2	8	3.83	4.8	1.25	4	18.76	65.3	3.38	
3	9	3.98	10.4	2.61	5	18.57	65.8	3.54	
4	10	3.72	10.7	2.87	6	17.29	64.8	3.74	(Dog cannot stand.)
5	11	3.31	11.7	2.71		21.45	77.5	3.61	100 gm. meat.
6	12	3.91	10.8	2.76		18.17	71.1	3.91	100 " "
7	13	3.89	11.2	2.87		18.30	66.7	3.64	100 " "
8	14	4.53	13.6	3.0		17.63	69.0	3.91	100 " "
9	15	3.63	9.5	2.62		16.06	62.0	3.80	100 " "
10	16	3.16	9.2	2.92		15.80	57.7	3.65	100 " " + 25 gm. lard.
11†	17	3.53	7.6	2.15		4.54§	16.9	3.72	100 " "

* Pancreatectomy.
† Exitus mortalis.
‡ Phlorhizin 3 times daily hereafter.
§ 6¾ hours' urine. Condition better than on the 6th day of fasting. Killed. Liver glycogen = 0.08 per cent.

The protein metabolism in phlorhizin diabetes rose to 450 per cent. and in pancreas diabetes to 233 per cent. of the fasting level. The larger increase, however, is not due to the action of phlorhizin *per se*, because in the fasting phlorhizinized goat,[1] which manifests a D:N ratio of 2.8:1, the protein metabolism rises to only 238 per cent. of the normal. The greater increase is due to the fact that carbohydrate is withdrawn from protein in larger measure in the phlorhizinized dog than in the depancreatized dog. The great waste of body tissue which arises in severe cases of uncontrolled diabetes mellitus is due to this increased protein metabolism.

It is noted in the table that on the fourth day of phlorhizin diabetes the dog could not stand. Strength and vigor were largely restored by giving 100 gm. of meat. Deuel and Chambers[2] noted that if 16 gm. of glucose were given to dogs in this lethargic state the general condition of the animals was markedly improved and their muscular power increased. Wierzuchowski[3] was the first to observe that, if the phlorhizinized dog on the fifth day of fasting and diabetes had a blood sugar of 0.06, it was liable to convulsive seizures; that it

[1] Lusk, G.: Z. f. Biol., 1901, **42**, 43.
[2] Deuel, H. J., Jr., and Chambers, W. H.: J. Biol. Chem., 1925, **65**, 7.
[3] Wierzuchowski, M.: *Ibid.*, 1926, **67**, p. xlii.

lay in a state of diabetic coma with aceton breath and with a low CO_2 combining power of the blood. The strength returned in 10 minutes as if by magic when glucose was administered. Within 4 hours acetonuria had vanished and the CO_2 combining power had returned to its normal level. Wierzuchowski[1] rightly attributed this result to the oxidation of a small quantity of the sugar ingested, and this has been confirmed by Deuel, Wilson, and Milhorat.[2] The condition of prostration returns within 24 hours in a dog so treated. If one reflects upon Ringer's table on p. 444 which shows the progressive decline in the glycogen content of the muscle in phlorhizin diabetes, one may well believe that a part of the ingested glucose may have caused a revival in the power of the dog's muscles by temporarily adding to their glycogen supply. (See p. 322.)

The Immediate Effect of Pancreatectomy as Regards the D:N Ratio.— Chambers and Coryllos[3] have investigated the concurrent changes in the level of the blood sugar and the urinary elimination of glucose and nitrogen in hourly and 3-hour periods during the 24 hours immediately following pancreatectomy. The blood-sugar rose within 2 hours after the operation. An initial rise in nitrogen elimination corresponded to a similar rise after partial removal of the pancreas and represents the absorption of blood and wound tissue from the operative procedure. Sugar appeared in the urine in 6 to 12 hours after the operation. At this point the nitrogen elimination rose sharply. The D:N ratios reached their maximum height about the 15th to 18th post-operative hours and gradually declined to the 2.8 level within 2 or 3 days. These early high D:N ratios indicate the mobilization of glycogen and especially liver glycogen, for the liver of the depancreatized dog cannot hold glycogen (see p. 619) unless insulin is administered. In one case, as shown in the table on p. 636, a D:N ratio of 5.4 was found in the urine of the 16th to the 19th hours after pancreatectomy.

[1] Wierzuchowski, M.: J. Biol. Chem., 1926, **68**, 385.
[2] Deuel, H. J., Jr., Wilson, H. E. C., and Milhorat, A. T.: *Ibid.*, 1927, **74**, 265.
[3] Chambers, W. H., and Coryllos, P. N.: Am. J. Physiol., 1926, **78**, 270.

THE BLOOD SUGAR AND THE URINARY D:N RATIO AFTER PANCREATECTOMY IN THE DOG

Hours after Operation	Blood Sugar	Urine per Hour		
		D	N	D:N
	Per Cent.	Gm.	Gm.	
(Before)	0.080	....	0.164	
2	0.103	....	0.158	
3	.....	....	0.199	
4	0.109	..	0.217	
8	0.171	....	0.213	
10–13	0.202	+	0.242	
13–16	0.178	0.79	0.331	2.37
16–19	0.162	1.96	0.364	5.37
19–22	0.227	1.98	0.378	5.25
22–25	0.244	1.84	0.392	4.68
25–49	0.236	1.45	0.298	4.87
49–60	.....	1.10	0.345	3.18
60–63	.....	1.20	0.343	3.50
63–73	0.253	0.76	0.273	2.77

Similar ratios have been found by Chaikoff[1] when the administration of 16 units of insulin and a diet of meat and cane sugar were withdrawn from the treatment of completely depancreatized dogs. The results appear in the following summary:

	Dog F		Dog C		Dog T	Dog D
	I D:N	II D:N	I D:N	II D:N	D:N	D:N
Second 12 hours	6.60	5.25	9.33	6.58	6.8	5.3
Third 12 "	4.70	2.70	....	....	4.22	3.1
Fourth 12 "	4.17	2.85	5.10	3.29	3.23	3.0
Fifth 12 "	3.38	3.02	4.53	2.88	3.27	1.9
Sixth 12 "	2.37	3.17	5.30	2.63	....	2.1

In all but one of these dogs standard Minkowski D:N ratios were obtained before the 3d day following the withdrawal of food and insulin. The picture here reproduced is identical with that found by Chambers and Coryllos. But high D:N ratios obtained under such circumstances indicate that stored liver glycogen and not fat is the source of the extra glucose.

The Immediate Effect of the Injection of Phlorhizin as Regards the D:N Ratio.—Deuel, Wilson, and Milhorat investigated the course of phlorhizin glycosuria in hourly periods following the injection of the drug into dogs 18 hours after the ingestion of the standard maintenance diet of the laboratory plus 50 gm. of cane sugar. Normally

[1] Chaikoff, I. L.: J. Biol. Chem., 1927, **74**, 203.

dogs so fed manifest in the post-absorptive state respiratory quotients of unity. The injection of phlorhizin at this time does not change the respiratory quotient for several hours. Phlorhizin was supplied in alkaline solution as well as in oil in order to furnish it quickly in large amounts to the kidney and to the tissues.

An abridged table of the urinary excretion follows:

THE BLOOD SUGAR AND THE URINARY D:N RATIO AFTER 1 GM. PHLORHIZIN IN OIL AND 1 GM. PHLORHIZIN IN 1 PER CENT. Na_2CO_3 SOLUTION INJECTED INTO A DOG RICHLY FED WITH CARBOHYDRATE 18 HOURS PREVIOUSLY. PHLORHIZIN INJECTIONS CONTINUED ONCE DAILY

Hours after Phlorhizin	Blood Sugar	Urine			Extra Glucose
		D	N	D:N	
	Per Cent.	Gm. per Hr.	Gm. per Hr.		Gm. per Hr.
Before	0.108	....	0.165		
1	.....	2.65	0.194	13.25	1.94
3	0.105	3.21	0.183	17.54	2.54
6	0.100	2.94	0.178	16.53	2.29
9	.....	2.79	0.185	15.09	2.12
12	0.101	2.79	0.208	13.43	2.04
15	0.086	2.32	0.284	8.17	1.28
18	0.077	1.96	0.408	4.80	0.34
24	0.082	2.24	0.484	4.63	0.47
25–43	0.093	2.36	0.577	4.10	0.26
44–67	0.059	2.40	0.595	4.03	0.23
68–95	0.055	1.89	0.505	3.73	0.04

In another dog which was fed and treated with phlorhizin exactly in the same manner as the last-mentioned animal the respiratory quotients obtained in successive hours and the calculations of glucose oxidized, were found to be as follows:

METABOLISM OF A DOG AFTER PHLORHIZIN
(Body weight, 10.1 kilos)

Hours after Phlorhizin	1	2	3	4	5	6	7	8	9	10
Non-protein R. Q.	1.01	1.01	0.93	0.93	0.97	0.97	0.93	0.85	0.99	0.94
Glucose oxidized, gm.	2.30	2.30	1.93	1.93	2.28	2.28	2.20	1.59	2.39	1.85

Hours after Phlorhizin	11	12	13	14	15	16	17	18–26	27
Non-protein, R. Q.	0.77	0.80	....	0.83	0.77	0.74	0.74	.....	0.69
Glucose oxidized, gm.	0.71	0.94	1.08	1.22	0.66	0.44	0.44	3.15*	0.00

* Estimated.

	Gm.		Per Cent.
Total glucose oxidized	29.7	=	47
" extra glucose excreted	33.8	=	53
Grand total	63.5		

One may therefore conclude that the equivalent of 63.5 gm. of glucose were originally present in the well-fed dog when phlorhizin was administered. For the body weight 63.5 gm. is 0.63 per cent. which corresponds to 0.57 per cent. of glycogen. In three well-nourished dogs Schöndorff[1] found between 0.58 and 0.76 per cent. of glycogen. In other dogs even higher values were found.

The results obtained in the living animal are therefore entirely comparable to those obtained from the dead animal, and we may conclude that the extra sugar eliminated during the periods of the high preliminary D:N ratios in phlorhizin glycosuria are exclusively attributable to the elimination of carbohydrate which was preformed in the body and are not due to an origin of sugar from fat.

The Cause of the Different Ratios.—Nothmann,[2] in a valuable article from Minkowski's clinic has demonstrated the presence of insulin in all the tissues of a normal dog and the absence of it in all the organs of a depancreatized dog with the sole exception of the liver, in which it may persist for weeks. Liver insulin extracted from a depancreatized dog will, on injection into another depancreatized dog, be a complete remedy for the diabetic condition of the latter. Nothmann states that the difference between Minkowski's ratio of 2.8 and Lusk's of 3.65 may lie in the fact that the liver of the depancreatized dog may be able to oxidize a certain quantum of the glucose or glucose precursors produced from protein which escapes oxidation in the phlorhizinized dog.

Though not established with certainty, this theory is the best yet offered in explanation of the two levels of sugar production from protein.

Criticism of the D:N Ratio.—The D:N ratio of 3.65:1 was accepted by Lusk as being true for the dog because the greater number of the higher ratios which were found were established at this level. Janney[3] prefers to take the average of all determined D:N ratios and in this way arrives at a ratio of 3.43:1. He argues that, since 4.7 per cent. of the urinary nitrogen is in the form of creatin and creatinin, which are not glucose formers a correction would bring up the D:N ratio in the dog to 3.60. Although it is not clear why the urinary creatin and creatinin should be thus subtracted, for they

[1] Schöndorff, B.: Pflüger's Arch. gesam. Physiol., 1903, **99**, 191.
[2] Nothmann, M.: Arch. exper. Path. u. Pharm., 1925, **108**, 1.
[3] Janney, N. W., and Csonka, F. A.: J. Biol. Chem., 1915, **22**, 203.

are as truly metabolism products of protein as is urea, still Janney's[1] experiments, which show the quantities of glucose produced from various forms of flesh, as determined through feeding experiments with the phlorhizinized dog, are of great interest and may thus be presented:

Species of Flesh	Man	Dog	Rabbit	Ox	Chicken
D:N ratio	3.6	3.6	3.8	3.6	3.4
Glucose per 100 gm. of protein metabolized	58	58	60	58	54

According to Janney,[2] the percentage quantity of glucose derivable from the following proteins is: casein 48, ovalbumin 54, serum albumin 55, gelatin 65, fibrin 53, edestin 65, gliadin 80, and zein 53 per cent.

THE HYPOTHESIS THAT FAT IS TRANSFORMED INTO GLUCOSE IN DIABETES

Pflüger[3] believed that fat metabolism was the principal source of sugar in diabetes.

In preparing the last edition of this book (1917) it was thought that sufficient evidence had been here assembled to demonstrate that fat was not transformed into glucose. Alleged proofs of such conversion are now in nearly all the textbooks and are widely believed by men of high scientific standing. It may be well to survey some of these proofs.

1. Hartogh and Schumm's[4] phlorhizinized dogs are widely cited in the literature. Witness these results:

Weight	Food	Day of Diabetes	Urine		
			N	D	D:N
Kg.			Gm.	Gm.	
55	Fat, 204 gm.	3	4.89	52.1	10.7
	" 63 "	7	5.17	67.2	13.0

Another dog weighing 39 kg., made diabetic with phlorhizin, eliminated only 1.47 gm. nitrogen in the urine of one day! Contrast these nitrogen values with those obtained by Mandel and Lusk[5] from

[1] Janney N. W., and Blatherwick, N. R.: J. Biol. Chem., 1915, **23**, 77.
[2] Janney, N. W.: *Ibid.*, 1915, **20**, 321.
[3] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1905, **108**, 115.
[4] Hartogh and Schumm, O.: Arch. exper. Path. u. Pharm., 1901, **45**, 11.
[5] Mandel, A. R., and Lusk, G.: Am. J. Physiol., 1906, **16**, 129.

a dog weighing 40 kg. which, on the 7th day of fasting and the 4th day of phlorhizin, eliminated 29.3 gm. nitrogen and 107.7 gm. sugar, a D:N ratio of 3.61. Lusk[1] has elsewhere stated that the figures reported by Hartogh and Schumm are unobtainable in a good laboratory. We have never observed an increase in the D:N ratio after giving fat to the diabetic animal. Takao[2] confirms us in this view.

2. Geelmuyden's[3] hypothesis that acetic acid is convertible into glucose is based upon experiments on an animal receiving carbohydrate in its diet, of which the following is a type:

Day of Phlorhizin	D Gm.	N Gm.	D:N	
4	57.0	7.51	7.6	
5	55.1	8.15	6.8	
6	58.0	8.75	6.6	9.5 gm. acetic acid
7	65.3	9.37	7.0	

This experiment is offered in evidence with no reference to the clear-cut demonstration by Ringer and Lusk[4] that acetic acid cannot be transformed into extra glucose in the phlorhizinized dog. This has been repeatedly confirmed by Milhorat and Deuel[5] in our laboratory. After giving 14.5 gm. sodium acetate intraperitoneally these authors found no effect on the D:N ratios. In one experiment the periods were of 12 hours; foreperiod D:N = 3.56, acetate period D:N = 3.62, after period D:N = 3.60.

3. Finally, there are the oft cited references to the diabetic patient of Grafe and Wolf[6] who, when partaking of a diet exclusively of fat and protein, eliminated a urine in which the D:N ratio was 10:1. If this were accurate, it would demonstrate the production of sugar from fat.

Greenwald obtained similar results upon a hospital patient, but after confining her in a room by herself the D:N ratio promptly fell to 3.6. In Du Bois' clinic a diabetic patient under supervision was left by his nurse alone with a relative for one minute. Later, suspecting mischief, the nurse found two sandwiches in the patient's bed and two secluded in the recesses of his arm pits! There is no question that this is the nature of this variety of "proof" that diabetics produce sugar from fat.

[1] Lusk, G.: Ergeb. d. Physiol., 1912, **12**, 315.
[2] Takao, T.: Biochem. Z., 1926, **172**, 272.
[3] Geelmuyden, H. C.: Skan. Arch. Physiol., 1920, **40**, 211.
[4] Ringer, A. I., and Lusk, G.: Z. physiol. Chem., 1910, **66**, 106.
[5] Milhorat, A. T., and Deuel, H. J., Jr.: Proc. Soc. Exper. Biol. and Med., 1926–27, **24**, 667.
[6] Grafe, E., and Wolf, C. G. L.: Deut. Arch. klin. Med., 1912, **107**, 201.

Reasons against the idea that fat is convertible into glucose.—

(1) On giving meat in diabetes the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D:N ratio, and therefore the latter cannot be influenced by the *quantity* of fat burned. This is shown in a respiration experiment made by Mandel and Lusk[1] on a dog with phlorhizin glycosuria whose metabolism starving and after meat ingestion was as follows:

	D:N	Calories from Protein	Calories from Fat	Calories, Total
Fasting	3.69	80.2	274.4	354.6
300 grams meat	3.55	161.9	261.7	423.6

The protein metabolism doubled when meat was ingested, the fat metabolism fell, but the D:N ratio remained constant.

(2) *It has also been demonstrated that neither exposure to cold nor mechanical exercise, both of which result in a largely increased metabolism of fat, has any effect on the sugar output in pancreas diabetes*[2] *or in phlorhizin glycosuria*[3] *after depletion of the glycogen reserves.* Freund and Marchand[4] found that ten hours' exposure to the winter's cold greatly reduced the blood-sugar of a phlorhizinized dog. The writer found in a phlorhizinized dog which had been largely rid of glycogen by shivering and exercise that the composition of the urine was unchanged as the result of traveling 1500 meters in a revolving wheel, an effort which would have more than doubled the metabolism of fat during the hour when the exercise was taken (Exp. II). The animal was weak and the work was done at intervals of 5 minutes for work and 5 for rest. The analytic data for two-hour periods were the following:

	Glucose, Gm.	Nitrogen, Gm.	D:N
I. Rest	4.20	1.19	3.53
I. Work, 1500 meters during first hour	5.32	1.36	3.90
II. Rest	4.57	1.26	3.63
II. Work, 1500 meters during first hour	4.62	1.26	3.67

In experiment II exercise was without influence on the excretion of nitrogen. If, however, the animal contains residues of glycogen which as a result of exercise are converted into sugar and eliminated, then there is also an increased nitrogen elimination as the result of

[1] Mandel, A. R., and Lusk, G.: Am. J. Physiol., 1903, **10**, 54.
[2] Allard, E.: Arch. exp. Path. und Pharm., 1908, **59**, 111; Seo, Y.: *Ibid.*, p. 341.
[3] Lusk, G.: Am. J. Physiol., 1908, **22**, 163.
[4] Freund, H., and Marchand, F.: Arch. exp. Path. und Pharm., 1913, **73**, 276.

work (Exp. I). This is suggestive of a chemical union between glycogen and nitrogenous substances (see p. 405). This experiment has been often confirmed.

(3) The theory of the origin of sugar from fat was supported by Falta,[1] who found a largely increased sugar output after administering epinephrin to dogs with pancreas diabetes. High D:N ratios in diabetes were explained by Falta as being due to very great activity on the part of the adrenals which not only inhibits the internal secretion of the pancreas, but also causes a production of sugar from fat. However, Ringer,[2] working in the author's laboratory, found that if epinephrin be administered to a fasting phlorhizinized dog, although the first administration of the drug may bring about an elimination of extra sugar which may be discharged from the glycogen repositories of the body on account of the anemia of the tissues (see p. 620), a second injection may be entirely without influence on either the sugar or nitrogen elimination. The observation has been confirmed by Woodyatt,[3] by Palmer,[4] and by Seuffert and Hartmann.[5]

An experiment of Kramer, Marker, and Murlin[6] presents in exact outline the effect of epinephrin upon the sugar secretion in a depancreatized dog weighing 12.4 kg.

Day after Pancreatectomy	D Gm.	N Gm.	D:N
11	27.57	8.97	3.07
12	20.05	6.89	2.90
13	45.45	8.96	5.07†
14*	25.67	9.70	2.64†

* 30 hours' urine.
† Adrenalin every 3 hours.

After a preliminary elimination of extra sugar derived from glycogen, further administration of epinephrin fails to evoke further sugar elimination. Here, in a condition of dire carbohydrate want, the production of glucose follows the usual rate at which it originates from protein.

[1] Eppinger, H., Falta, W., and Rudinger, C.: Z. klin. Med., 1908, **66**, 1.
[2] Ringer, A. I.: J. Exp. Med., 1910, **12**, 105.
[3] Woodyatt, R. T.: J. Biol. Chem., 1913, **14**, 441.
[4] Palmer, W. W.: *Ibid.*, 1917, **30**, 79.
[5] Seuffert, R. W., and Hartmann, H.: Cremer's Beitr. z. Physiol., 1924, **2**, 199.
[6] Kramer, B., Marker, J., and Murlin, J. R.: J. Biol. Chem., 1916, **27**, 499.

Epinephrin therefore does not cause a production of sugar from fat.

Hildebrandt[1] rightly states that if after the injection of epinephrin there is no glycosuria in normal animals, this is a sign of the exhaustion of their glycogen supply.

The Possible Production of Glucose from the Glycerol of Fat.—Cremer[2] was the first to show that glycerol, when taken by a diabetic patient, increased the glucose in the urine. Chambers and Deuel[3] recovered 97 and 98 per cent. of glycerol, ingested by phlorhizinized dogs, as extra glucose in the urine.

When tri-palmitin is oxidized its respiratory quotient is 0.703 (see p. 63). If by hydrolysis it loses glycerol, the respiratory quotient of the palmitic acid would be 0.696, as calculated for me by A. I. Ringer. Tri-palmitin yields 11 per cent. of glycerol. In the experiment mentioned on p. 641 the diabetic dog oxidized in fasting during 24 hours 58.2 gm. of fat, and after meat ingestion 55.4 gm. of fat. Assuming that the fat yields 10 per cent. of glycerol, we have 5.82 and 5.54 gm. derivable daily from this source. We now have the data for modifying the D:N ratio:

	D	N	D:N	D from Glycerol	D from Protein	Possible D:N
Fasting	53.04	14.36	3.69	5.82	47.22	3.29
300 gm. meat	74.37	21.00	3.54	5.54	68.83	3.28

The difficulty with this method of computation lies in the fact that when mechanical work is done, which largely increases the fat metabolism, there may be no change in the D:N ratio. It seems, therefore, that *glycerol originating from fat in diabetes is oxidized with the fatty acid simultaneously liberated.* It is known that the glycerol is there and that it may not appear after exercise as extra sugar. By the same token it may be argued that fatty acid is continually passing into sugar and being instantaneously oxidized even in diabetes. But of this there is no fragment of evidence, and I have chosen to call it a figment of the imagination.

THE INTERRELATION OF INTERNAL SECRETIONS IN DIABETES

Falta explained the results of many experiments by stating that, while the secretory activities of thyroid and adrenals are each stimu-

[1] Hildebrandt, F.; Arch. ex. Path. u. Pharm., 1920, **88**, 80.
[2] Cremer, M.: Münchener med. Wochenschr., 1902, **49**, 944.
[3] Chambers, W. H., and Deuel, H. J., Jr.: J. Biol. Chem., 1925, **65**, 21.

lated by the secretions of the other, the activity of the pancreas is in like manner inhibited by the secretions of the other two glands. Therefore supersecretion of epinephrin inhibits the secretory function of the pancreas so that the organism can no longer oxidize carbohydrates, and at the same time it stimulates the thyroid, causing increased protein metabolism. Furthermore, in exophthalmic goiter, where there is supersecretion in the thyroid gland, there is a tendency to glycosuria, and it is believed that true diabetes has been induced by this cause.[1] Administration of thyroid extracts to dogs also produces glycosuria. Cecil,[2] working under Opie's direction, finds lesions of the pancreas in cases of diabetes associated with exophthalmic goiter, and Forschbach and Severin,[3] in Minkowski's clinic, believe that there is very likely a slight disturbance of the pancreas in some cases of hyperthyroidism.

The complicated theorizing of the von Noorden school, as represented by Falta's statements, found early acceptance among clinicians. However, there are many demonstrable errors in the presentation. Thus Ringer, in the experiments mentioned above, found no increase in the protein metabolism of his dogs after giving them epinephrin, and Lusk[4] found the same to be true in normal dogs, and also discovered that if glucose were given to normal dogs and then epinephrin were administered the respiratory quotient rose to unity, showing a normal combustion of carbohydrate.

Fuchs and Róth[5] and many others state that the respiratory quotient increases in human beings after the subcutaneous injection of epinephrin, as appears below:

Before	Epinephrin	After
0.85	*0.91*	0.84
0.87	*0.96*	0.86

It is evident that the theory that epinephrin causes a production of sugar from fat, decreases the power of the organism to oxidize glucose through inhibition of pancreatic function, and stimulates the thyroid so that protein metabolism is increased, is untenable in any of its particulars.

[1] Magnus-Levy, A.: von Noorden's "Handbuch der Pathologie des Stoffwechsels," Berlin, 1907, **2**, p. 333.
[2] Cecil, R. L.: J. Exp. Med., 1909, **11**, 266.
[3] Forschbach, J. and Severin, J.: Arch. exp. Path. und Pharm., 1914, **75**, 168.
[4] Lusk, G.: Arch. Int. Med., 1914, **13**, 673.
[5] Fuchs, D., and Róth, N.: Z. ex. Path. und Ther., 1912, **10**, 187.

In the matter of the thyroid being the cause of the high protein metabolism in diabetes, von Noorden is right. Eppinger, Falta, and Rudinger[1] extirpated both pancreas and thyroid and found that the protein metabolism was almost the same as in the normal dog instead of being increased three- or fourfold, as occurs when the pancreas alone is extirpated. The D:N ratio was at first 3.5, but declined after a few days to 2.8.

Von Noorden suggested to the writer of this book that the increased total metabolism which follows the administration of phlorhizin (see p. 634) would not take place if the thyroid gland had been previously extirpated. Lusk[2] determined the metabolism of a dog after complete thyroidectomy with removal of three parathyroids and found it to be 19 calories per hour, whereas after phlorhizin administration values of 20.3 and 19.3 calories per hour were found, determined one and three days after diabetes had been induced. The usual rise in protein metabolism and total metabolism was absent. After the ingestion of meat, however, the heat production increased and rose on one occasion from a basal value of 17.5 to 26 calories per hour, an increase of 50 per cent. The urinary nitrogen largely increased and the process of amino-acid stimulation was in full play, notwithstanding the absence of the thyroid gland. This naturally confirms the hypothesis that the reason why there is no increased heat production in diabetes after thyroidectomy is that there is no rise in the quantity of protein metabolized.

As shown by Parhon and by Cramer (see p. 600), thyroid ingestion causes the liver to discharge glycogen. Conversely, after thyroid extirpation the liver should retain glycogen more tenaciously than before. This, at least, would explain the long continued high D:N ratios observed by Lusk in phlorhizinized dogs after thyroidectomy and by Miura[3] in rabbits similarly treated.

In contradiction to the statements of Eppinger, Falta, and Rudinger, and of Miura, Underhill[4] finds that epinephrin glycosuria may be as easily produced in thyroidectomized as in normal animals.

The subject of the correlation between the various glands of internal secretion is evidently one as replete with opportunities for

[1] Eppinger, H., Falta, W., and Rudinger, C.: Z. klin. Med., 1908, **66**, 1.
[2] Lusk, G.: Proc. XVIIth International Congress of Medicine, Section on Physiology, London, 1913, p. 13.
[3] Miura, S.: Biochem. Z., 1913, **51**, 423.
[4] Underhill, F. P.: Am. J. Physiol., 1910–11, **27**, 331.

the play of the imagination as it is for enlightening experimental research.

Nearly twenty years have passed since the school of von Noorden gave utterance to its theories, and they are mentioned now because they have found an abiding place in the minds of men.

Falta[1] at the present time believes that in cases of hyperglycemia, whether alimentary in origin or due to intravenous glucose injections or to administration of epinephrin, there is a stimulation of the islet apparatus for the production of insulin. The influence of this insulin is to lessen the output of sugar from the liver and to increase the receptivity of all the peripheral tissues for glucose, incidentally raising the respiratory quotient. Falta has come to the conclusion that the activities of insulin, epinephrin, and thyroxin are normally in balanced equilibrium one with another, and disturbance of this balance means disturbed carbohydrate metabolism.

Thus in typical diabetes there is insufficient activity of the islet apparatus and an over activity of the adrenal. Hypoglycemia produced by insulin is stated to be due to the avidity of the tissues for carbohydrate. Every hypoglycemia decreases the production of insulin and produces through the adrenals an automatic counter-regulation which lowers the avidity of the cells for sugar and promotes the discharge of liver sugar. Falta suspected this in 1924 when he found a heightened susceptibility to insulin in a patient with diabetes complicated with Addison's disease, the latter being a disease which is due to the insufficiency of the chromaffin system. Arnett[2] reports a similar case.

It was, however, in 1924 that Cannon[3] stated that the hypoglycemic reactions after insulin, such as pallor, rapid pulse, dilatation of the pupils, and profuse sweating, resembled the results of the discharge of sympathetic influences. Cannon denervated a living cat's heart, which then became hypersensitive to epinephrin. When insulin hypoglycemia was produced in such an animal the heart beat faster. If the post-insulin level of 70 mg. of glucose per 100 c.c. blood were restored to normal by glucose injections the heart beat normally. If the adrenals were removed, insulin hypoglycemia had no effect on the rate of the denervated heart and convulsive seizures took place more quickly. Cannon therefore concluded that hypoglycemia

[1] Falta, W.: Klin. Wochenschr., 1927, **6**, 835.
[2] Arnett, J. H.: Arch. Int. Med., 1927, **39**, 698.
[3] Cannon, W. B., McIver, M. A., and Bliss, S. W.: Am. J. Physiol., 1924, **69**, 46.

caused sympathetic activity with adrenal secretion and sugar mobilization from the liver in order to provide for the sugar needs of the blood. The second stage of augmentation was met by convulsive seizures and the discharge of sugar from muscle glycogen. The arrangement represents another remarkable example of automatic adjustment when a disturbance threatens the equilibrium of the organism.

Wilder[1] has analyzed 38 patients having diabetes and hyperthyroidism and one case of diabetes with myxedema. He finds that diabetes exists in only 1.1 per cent. of all cases of hyperthyroidism. A mild and inconspicuous case of diabetes, however, may be fanned into a flame by hyperthyroidism. The requirement for insulin is increased by the heightened metabolism. Thyroidectomy is almost always followed by a gain in sugar tolerance, and sometimes by apparent cure, though the diabetes remains latent, as shown by tolerance tests. The state of myxedema may abolish diabetes, which returns when the patient is restored to a normal level of basal metabolism. Wilder states that it would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement for insulin is disproportionately increased. He considers it unnecessary to speculate regarding a specific interdependence of thyroid and pancreas. Exercise which increases total metabolism does not decrease sugar tolerance, hence there must be a fundamental difference between metabolism attending muscular contraction and metabolism associated with food ingestion and agents like thyroxin.

ADDISON'S DISEASE. BEHAVIOR OF EPINEPHRIN

So much has been said regarding the behavior of epinephrin in relation to diabetes that it seems opportune at this point to make brief mention of the physiological action of the adrenal gland from which it arises.

In Addison's disease, which is usually associated with a tuberculous adrenal, the blood sugar was found to be low by Porges.[2] The antidoting action of epinephrin which raises the blood sugar in the presence of insulin hypoglycemia (see p. 646) is absent. A patient of Rowntree reported by Muirhead[3] showed a basal metabolism of 15

[1] Wilder, R. M.: Arch. Int. Med., 1926, **38**, 736.
[2] Porges, O.: Z. klin. Med., 1909–10, **69**, 341.
[3] Muirhead, A. L.: J. Am. Med. Assn., 1921, **76**, 652.

to 30 per cent. below the normal. Means (quoted by Aub, Forman, and Bright) found a value of −15 per cent. in a patient with Addison's disease.

Aub, Forman, and Bright[1] have described how cats, 48 hours after the removal of the adrenal glands, manifest a reduction in metabolism of 25 per cent. Aub, Bright, and Forman[2] furthermore show that this fall in metabolism takes place after prior removal of the thyroid gland and hence the thyroid has nothing to do with the reaction. If at this point epinephrin be introduced at the usual physiological rate of its production, the metabolism increases. These authors concluded that epinephrin effects a quick, almost immediate, response and thyroxin a slower one, a finding also emphasized by Boothby (see p. 605).

Boothby and Sandiford[3] have accomplished a strikingly fine piece of work regarding the calorigenic action of epinephrin chlorid upon human beings. They compared the increase in metabolism after giving 100 gm. of glucose with that obtained after the subcutaneous injection of 0.5 mg. of epinephrin, with the following results:

	41 Experiments 100 Gm. Glucose		22 Experiments 0.5 Mg. Epinephrin	
	Before	After	Before	After
Basal metabolism, per cent	100	109	100	120
Blood sugar, per cent	0.132	0.271	0.143	0.196
Blood sugar increase, per cent	.....	105	.....	37
R. Q.	0.77	0.93	0.77	0.87

Following epinephrin injection, a rise of 37 per cent. in the quantity of blood-sugar was associated with an increase in metabolism of 20 per cent., whereas following glucose ingestion a rise of 105 per cent. in the blood-sugar caused an increase in metabolism of only 9 per cent. The increased heat production after epinephrin was therefore not due to a plethora of carbohydrate particles but to a true effect upon the cells, which raised their power to metabolize. Furthermore, in a case of complete diabetes complicated with exophthalmic goiter, with a basal metabolism of +80 per cent., epinephrin given subcutaneously increased the basal metabolism to a level of +149 per

[1] Aub, J. C., Forman, J., and Bright, E. M.: Am. J. Physiol., 1922, **61**, 326.
[2] Aub, J. C., Bright, E. M., and Forman, J.: *Ibid.*, p. 349.
[3] Boothby, W. M., and Sandiford, I.: *Ibid.*, 1923, **66**, 93.

cent. without any oxidation of sugar taking place. Epinephrin, therefore, has no specific action on carbohydrate oxidation.

Krantz and Means[1] find, after giving epinephrin intramuscularly to obese and to normal subjects, that in the obese the respiratory quotients scarcely rise, for epinephrin acts to increase the oxidation of the food most readily available and in obesity this is fat.

[1] Krantz, C. I., and Means, J. H.: J. Clin. Invest., 1927, **4**, 225.

CHAPTER XXV

DIABETES MELLITUS

Before hazarding a theory we propose to multiply our observations, to investigate the phenomena of digestion, and to analyze the blood both in health and in disease. We will draw upon medical records and the light and experience of learned physicians who are our contemporaries, and it will be only when we are thus completely armed that we will dare to attack a revered and antique colossus of prejudice and error.—LAVOISIER, in his last memoir before the Académie des Sciences, in 1790.

IN the early summer of 1921 Banting, filled with the idea of obtaining the active pancreatic hormone, went to Macleod's laboratory at Toronto, Canada. Best, then a second year medical student, was employed as assistant in the undertaking. Banting and Best produced effective extracts curative of human diabetes. Collip, a first-rate chemist, later joined the group and was able for the first time, with exactitude and certainty, to extract a potent, efficient anti-diabetic hormone from the pancreas, one which could be used in the clinical treatment of diabetes mellitus.[1]

The remarkable phenomenon of an emaciated boy, dying in diabetic coma, transformed into a healthy well-nourished lad within a period of 3 months[2] through the injection of insulin presents just one example of this precious gift to humanity. One should not forget that the resources of the Eli Lilly Company and the advice of their chief scientific expert, C. H. A. Clowes, made insulin commercially possible. Nor will it be quickly forgotten that this firm has generously contributed the product gratis to scientific workers the world over.

It may be here recorded that Naunyn, justly celebrated for his dietetic treatment of diabetes mellitus, when he heard of the discovery of insulin, wrote to Minkowski advising him not to believe it, that it was another case of American "bluff."

It is scarcely necessary to say that others had attempted and nearly succeeded in accomplishing what Banting and his colleagues

[1] Banting, F. G., and Best, C. H.: J. Lab. and Clin. Med., 1922, **7**, 251, 464; Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.: Trans. Roy. Soc. Canada, 1922, Sec. V, **16**, 28; a full review by Macleod, J. J. R., and Campbell, W. R.: "Insulin," Medicine Monographs, Baltimore, 1925, and by Laqueur, E.: Jahresber. ges. Physiol., 1924, **5**, 677.

[2] Major, R. H.: J. Am. Med. Assn., 1923, **80**, 1597.

actually achieved. Witness the work especially of Gley,[1] Zuelzer,[2] Scott,[3] Murlin and Kramer,[4] and Kleiner.[5] Thus Gley, prior to 1905, had injected the ducts of the pancreas with oil and had induced sclerosis of the glandular tissue without producing diabetes. He therefore concluded that the islands of Langerhans yielded an internal secretion. Extracts of a pancreas thus treated lowered the sugar output of diabetic dogs. He stated that extracts of the whole gland masked the effect. Had Gley at once published his important discovery, the finding of insulin would not have been so long delayed. At a meeting in Germany at which Zuelzer set forth his claims of priority Minkowski arose and said, "I too share with Professor Zuelzer the regret that I did *not* discover insulin."

The workers at Toronto early showed that their extracts of the pancreas could raise the respiratory quotients of diabetic dogs, as Murlin and Kramer had also shown.

The reduction of the D:N ratio in diabetic dogs shown by Zuelzer, Scott, and by Kleiner has recently been beautifully analyzed by von Falkenhausen,[6] as appears in the following table:

A COMPARISON BETWEEN THE D:N RATIOS IN DOGS AFTER (1) PANCREATECTOMY, (2) PARTIAL PANCREATECTOMY, AND (3) PANCREATECTOMY PLUS 3 UNITS OF INSULIN 3 TIMES DAILY

(1) Wt., 14.5 Kg.		(2) Wt., 6.8 Kg.		(3) Wt., 11.4 Kg.	
Urine		Urine		Urine	
N	D:N	N	D:N	N	D:N
Gm.		Gm.		Gm.	
2.98	....	†	....	9.23	2.83
*	....	4.28	1.33	7.63	2.09‡
6.83	2.70	3.68	0.95	7.28	1.39
6.32	3.02	3.76	0.63	5.96	1.05
7.21	2.80	3.49	0.74	5.28	0.45
7.08	2.99	2.28	0	4.86	0

* Pancreatectomy.
† Partial pancreatectomy.
‡ Insulin begun on this 3d day after pancreatectomy.

[1] Gley, E.: Sealed statement of 1905: published Compt. rend. soc. biol., 1922, **87**, 1322.
[2] Zuelzer, G.: Z. exper. Path. u. Therap., 1908–09, **5**, 307.
[3] Scott, E. L.: Am. J. Physiol., 1911–12, **29**, 306; J. Am. Med. Assn., 1923, **81**, 1303.
[4] Murlin, J. R., and Kramer, B.: J. Biol. Chem., 1913, **15**, 365; 1916, **27**, 517.
[5] Kleiner, I. S.: *Ibid.*, 1919, **40**, 153; 1920, **41**, p. xviii.
[6] von Falkenhausen, M.: Arch. exper. Path. u. Pharm., 1925, **109**, 249.

These results deserve careful study, for in them lies the essence of important factors in diabetic knowledge.

The influence of insulin in relation to the intermediary carbohydrate metabolism has been elsewhere discussed (see p. 338).

INFLUENCE OF INSULIN ON OXIDATION

The influence of insulin on carbohydrate metabolism has been dealt with elsewhere in this book. The insulin literature is so vast that it is difficult to choose the most desirable illustrations of its action. The following table given by Rabinowitch[1] was the result of early insulin work when the material was rare. Beautiful insulin effects on the diabetic are also described by John.[2]

EFFECT OF 16 UNITS OF INSULIN ON A PATIENT WITH SEVERE DIABETES

Time	R. Q.	Urine Sugar	Blood Sugar	CO_2 Combining Power	Blood Aceton
		Gm.	Per Cent.	Vol. Per Cent.	Mg. in 100 C.C.
9:30	0.72	....	0.28	39.3	104
9:45	0.75	0.60	0.24	39.6	87
10:00	0.76	0.64	0.22	40.2	73
10:15	0.78	0.48	0.21	40.8	74
10:30	0.79	0.28	0.19	42.4	56
11:30	0.79	0.11	0.12	42.2	44
12:30	0.80	0.18	0.08	44.4	39

It will be observed that because of the administration of 16 units of insulin to this patient with severe diabetes, glucose was oxidized as manifested by (1) a rise in the respiratory quotient, (2) a fall in the blood sugar, (3) a fall in the urine sugar, (4) a fall in the aceton bodies in the blood, with a consequent (5) rise in the CO_2 combining power of the normal blood. In other words, the diabetic metabolism assumed a normal character.

Boothby and Weiss[3] have discovered that after they gave a diabetic man 30 units of insulin the blood sugar fell from 190 mg. per 100 c.c. of blood to 70 mg. within 140 minutes during which period the heat production remained at a constant level. When the hypoglycemic level of 69 mg. of blood sugar was reached the metabolism suddenly rose. This phenomenon, which also occurs in dogs, may be the

[1] Rabinowitch, I. M.: Arch. Int. Med., 1923, **32**, 796.
[2] John, H. J.: *Ibid.*, 1927, **39**, 67.
[3] Boothby, W. M., and Weiss, R.: J. Biol. Chem., 1925, **63**, 1.

consequence of an output of adrenalin which occurs in hypoglycemia (see p. 646).

The further literature regarding the influence of insulin upon the quantity and quality of the metabolism is somewhat contradictory. Hawley and Murlin[1] determined the basal metabolism of large quietly resting Belgian hares and witnessed an increase in the basal metabolism of 16 per cent. during the 1st hour, an increase which was at the expense of fat, for the respiratory quotient did not rise. In the 2d hour the metabolism maintained the same higher level but at the expense of the oxidation of carbohydrate.

Chaikoff and Macleod[2] state that when normal rabbits received ample carbohydrate in their food insulin does not affect the heat production nor increase carbohydrate oxidation, while in the fasting condition insulin increases the oxidation of carbohydrate and the total heat production 10 per cent.

Chambers, Deuel, and Milhorat[3] administered amytal to dogs, determined their metabolisms 48 hours after food, and then administered insulin and recorded the results. The same authors[4] had previously shown that this hypnotic (which has no influence upon the blood sugar level[5]) slightly lowers the basal metabolism (see p. 753), which then remains at an even level for several hours. The results are summarized below:

EFFECT OF INSULIN DURING AMYTAL ANESTHESIA

	Before Insulin		Units of Insulin	After Insulin	R. Q. Hours after Insulin				Blood Sugar at the End
	Calories	R. Q.		Calories	2	3	4	5	
	Per Hour		Per Kg.	Per Hour					Per Cent.
Dog 30	12.9	0.74	6	16.1	0.78	0.89	0.75	0.76	0.042
" 28	19.9	0.72	5	18.0	0.72	0.86	0.73	0.72	0.006
" 33	23.5	0.78	5	29.7	0.78	0.78	0.75	0.69	0.031
" 30	11.0	0.73	7	11.4	0.75	0.72	0.75	0.70	0.028
" 34	18.8	0.72	5	17.3	0.76	0.78	0.78	0.79	0.037
Average	17.2	....	..	18.5					

In 2 of 5 dogs the metabolism increased. In 3 of 5 dogs the respiratory quotient rose in the 3d hour, but this effect was not very pronounced during any of the other hours. Possibly amytal in some of these cases prevented the calorigenic effect of epinephrin on the tissues. The CO_2 combining power of the blood was least in the 3d hour, and the blood sugar also reached its lowest level at this time. These reactions were common to all the dogs so that the higher respiratory quotients obtained from only three of them during the 3d hour were probably not due to the loss of CO_2 from the blood. In Dog 30 neither the heat production nor the respiratory quotients were increased after the administration of 7 units of insulin per kilogram to the animal under amytal anesthesia.

It appears, therefore, that in the course of insulin hypoglycemia, produced under amytal anesthesia, the total heat production may or may not be increased and likewise

[1] Hawley, E. E., and Murlin, J. R.: Am. J. Physiol., 1925–26, **75**, 107.
[2] Chaikoff, I. L., and Macleod, J. J. R.: J. Biol. Chem., 1927, **73**, 725.
[3] Chambers, W. H., Deuel, H. J., Jr., and Milhorat, A. T.: *Ibid.*, 1927, **75**, 423.
[4] Deuel, H. J., Jr., Chambers, W. H., and Milhorat, A. T.: *Ibid.*, 1926, **69**, 429.
[5] Page, I. H.: J. Lab. and Clin. Med., 1923–24, **9**, 194.

the oxidation of carbohydrate may or may not be increased. When there is no extra combustion of carbohydrate the sugar of the blood must be retired by the liver and lodged there in the form of glycogen.

Laqueur closes his review of the insulin problem up to 1925 by saying that if the reader is angry or disquieted by the discussion it cannot be laid to his door but to the problem itself; established facts have retreated to the background, and in the advance stand a multitude of hypotheses and theoretical discussions which give an unpromising outlook over the field.

It seems to be true that we matter-of-fact people on this side of the Atlantic have tried to shun the hypothetical and tried to establish the facts in our work upon the effect of endocrines upon the metabolism.

CRYSTALLINE INSULIN

Abel[1] and his collaborators have prepared from 2 gm. of a dry insulin powder, made in Toronto, a total of 0.528 gm. of crystalline insulin which is levogyrous and has a formula of $C_{45}H_{69}O_{14}N_{11}S$ and a physiological value of 40 international units per milligram. An international unit is "one-third of that amount which is necessary to lower the blood sugar to the convulsive level within a period of three hours in a rabbit of approximately two kilograms weight, from which food has been withheld 24 hours previous to ingestion" (definition of Macleod). This crystalline insulin, to the amount of 0.075 mg., would therefore cause convulsions in a rabbit weighing 2 kg. Two forms of crystals are obtained, of equal potency. It remains to be proved whether the crystals are insulin or are contaminated with insulin.

Synthalin.—Frank, Nothmann, and Wagner[2] report concerning a guanidin compound, synthalin, which reduces the level of blood sugar and causes the oxidation of glucose in diabetes. Its action is less constant than the action of insulin, and it may exert a toxic action on the liver and kidneys. Its further development will be awaited with interest. Professor Frank informs me that it consists of decamethylen diguanidin,

$$H_2N\overset{NH}{\overset{\|}{C}}HN(CH_2)_{10}NH\overset{NH}{\overset{\|}{C}}NH_2.$$

[1] Abel, J. J., Geiling, E. M. K., Rouiller, C. A., Bell, F. K., and Wintersteiner, O.: J. Pharm. and Exper. Therap., 1927, **31**, 65.

[2] Frank, E., Nothmann, M., and Wagner, A.: Deut. med. Wochenschr., 1926, **52**, 2067; Klin. Wochenschr., 1926, **5**, 2100.

THE PROTEIN METABOLISM

The use of insulin has saved many lives. We of an older day have been permitted to study patients when this drug was unavailable. Some of these patients behaved as though they had been completely depancreatized and could no longer oxidize sugar. Usually, however, the human diabetic behaves as though partial pancreatectomy had been performed, and in such a one dieting may completely relieve the symptoms. The background of complete diabetes deserves study.

For the treatment of diabetes and the consideration of its underlying philosophy the reader is referred to the fourth edition of the book on the subject by the master clinician Joslin.[1]

In the case of diabetes mellitus reported by Mandel and Lusk[2] in which the ratio D:N was 3.65:1, it was found that the ingestion of broths containing 7.7 grams of nitrogen was followed by an elimination of 21.7 grams of nitrogen in the urine or a loss of body nitrogen approximating 14 grams. The patient was greatly emaciated and passed this day in bed. He could not be maintained in nitrogen equilibrium with 19 grams of protein nitrogen in the food, but was in nitrogen equilibrium when taking 27 grams. In all cases of intense diabetes this factor of an increased protein metabolism must be considered. In mild cases in which sugar disappears from the urine when carbohydrates and protein are reduced in the food, and in which the patient may then oxidize his protein sugar, the protein metabolism is not different from that of a normal person living on such a diet.

As would be expected under conditions involving an increase in protein metabolism, amino-acids are found in increased quantities in both blood and urine of diabetic patients.[3]

Falta and Gigon[4] were the first to observe that in severe diabetes the body was more sensitive to protein than to sugar ingestion as regards its output of urinary sugar.

Gephart, Aub, Du Bois, and Lusk[5] reported concerning a diabetic man who had had the disease in a mild form and who showed a tolerance for 40 gm. of carbohydrate daily (that is to say, whose urine

[1] Joslin, E. P.: "The Treatment of Diabetes Mellitus," 4th ed., Philadelphia and New York, 1928.

[2] Mandel, A. R., and Lusk, G.: D. Arch. klin. Med., 1904, **81**, 491.

[3] Galambos, A., and Tausz, B.: Z. klin. Med., 1913, **77**, 14; 1914, **80**, 381. Löffler, W.: *Ibid.*, 1913, **78**, 483.

[4] Falta, W., and Gigon, A.: Verhandl. d. 24 Kongress. inn. Med., 1907, p. 256.

[5] Gephart, F. C., Aub, J. C., Du Bois, E. F., and Lusk, G.: Arch. Int. Med., 1917, **19**, 908.

was free from sugar while taking that quantity of carbohydrate). He became completely diabetic with a urinary D:N of 3.84: 1 on the 2d day after administering a diet containing considerable quantities of protein and fat. Subsequently, virtual starvation led in 60 hours to the disappearance of the sugar in the urine.

	Diet			D:N	R. Q.
	Protein N	CH	Total Calories		
	Gm.	Gm.			
	15	40	1500	0	0.79
1st day	25	3	3000	1.53	
2d "	25	3	3000	3.84	
3d " (12 hrs.)	12.7	2	1850	3.09	0.71
4th " Fasting and stolen bread					
5th " " " " "	....	..	....	0	0.78

It was thus proved that a potential diabetic could be transformed into a completely diabetic individual merely by administering the time-honored carbohydrate-free diet of meat and fat. It explained the production of the constant D:N ratio in the diet of Mandel and Lusk's diabetic man. (Compare results upon C. K. on p. 677.) It was quite as though one had administered phlorhizin.

Further verification of this may be read in the work of Wilder, Boothby, and Beeler[1] in as clear-cut a piece of metabolism artistry as may well be conceived.

Results characteristic of the various periods I have put together in the following table.

INFLUENCE OF HIGH PROTEIN IN THE DIET ON THE D:N RATIO IN HUMAN DIABETES

Period	II	III	IV	V	VI	X
Diet: P, gm.	0	46.9	94.2	103.6	9.9	104.8
CH, gm.	0	0.7	1.8	3.3	15.6	3.8
F, gm.	0	88.3	99.1	137.9	83.4	126.3
No. of days	2	5	4	5	10	4
Urine N, gm.	4.43	13.3	18.06	17.0	....	15.4
Urine D, gm.	0	25.5	51.4	67.6	0*	59.6
D:N	0	1.88	2.90	3.73	0	3.63
Basal metabolism, per cent	−27	−18	−14	−10	−20	−1
Aceton bodies, gm.	0.29	2.33	2.39	20.2	0	13.52‡
R. Q.	.....	0.70	0.70	0.69	0.72†	0.69

* 7th day of diet.
† 9th day of diet.
‡ 3d day of diet.

[1] Wilder, R. M., Boothby, W. M., and Beeler, C.: J. Biol. Chem., 1922, **51**, 311.

An initial fasting period (II) brought about a urine free from sugar, (III) moderate protein and high fat intake resulted in diabetes, (IV) doubling the protein produced a diabetes of considerable severity, (V) increasing the protein and fat still further brought about complete diabetes with D:N ratios of 3.41, 3.76, 3.98, 3.78 on four successive days. The last day of period V there was increasing acidosis, the patient was drowsy, with impending coma. A Newburgh diet (see p. 663) of low protein, low carbohydrate, and high fat (VI) was then administered, and on the 7th day the patient was free from urinary sugar and free from acidosis. Upon a second trial (X) of the diet high in meat and fat the D:N ratios reached 3.68, 3.62, 3.84, and 3.63 on 4 successive days.

The diet of period VI which checked the acidosis and resulted in the complete disappearance of diabetic symptoms was planned so that it contained 2 gm. molecules of fatty acid to one of glucose, or in other words, one of fatty acid to one triose molecule, whether derived from glycerol or from the cleavage of carbohydrate.

Thousands of investigations have been carried out upon the effect of this or that cure for diabetes without any realization that the mere reduction of the amount of protein given to the diabetic patient may be the sole cause of the beneficial result observed. Joslin many years ago privately informed me that he would not place a patient upon a diet of fat and protein alone on account of the deleterious effects which might be produced, and he has stated in personal conversations that fatal results might ensue if the diet were long continued. The results here cited show that Joslin was correct as regards the evil effect of even a moderately high protein intake upon the metabolism of the diabetic patient.

DIABETIC ACIDOSIS

The preëminence of fat metabolism in the diabetic as the mainstay of his organism leads to inquiry as to the origin of the fatty acid called β-oxybutyric acid, and of aceto-acetic acid and aceton which are directly derived from it.[1] Whence do these aceton bodies arise? They were at first supposed to come from glucose, following a chemical process analogous to the butyric acid fermentation of carbohydrates, but it was soon discovered that in normal persons the aceton bodies were especially found in the fasting state. Many then

[1] This description is taken from Lusk, G.: "Metabolism in Diabetes," Harvey Society Lecture, Arch. Int. Med., 1909, **3**, 1.

attributed the presence of aceton to the specific breakdown of body protein, since, when protein was given in the food, the aceton bodies disappeared in the urine. However, Magnus-Levy[1] has reported a case of a boy in coma who eliminated an average of 97.5 grams of β-oxybutyric acid and aceto-acetic acid daily for three days in addition to an unmeasured quantity of aceton in the breath, and during this time the protein metabolism amounted to 90 grams, of which latter at least 40 grams appeared as sugar in the urine. The 97.5 grams of aceton bodies in this case could not have been entirely derived from the 90 grams of protein, but they must have originated largely from fat.

Stadelmann[2] first pointed out the relationship between the formation of β-oxybutyric acid and the occurrence of coma. Coma has been compared to the Sword of Damocles which hangs suspended over every diabetic. It has been discovered that whenever the organism is thrown suddenly from a carbohydrate regimen to a combustion of fat the aceton bodies appear in the urine. This condition is greatly intensified in diabetes when even the sugar derived from protein is not oxidized.

Each molecule of butyric acid can yield one of β-oxybutyric acid. It has been calculated by Magnus-Levy[3] that 100 grams of neutral fat made of stearin, palmitin, and olein may yield 36.2 grams of β-oxybutyric acid. It is therefore evident that the higher fatty acids are the more valuable nutriment. Butter, with its high content of butyric acid, is said to increase the output of the aceton bodies in diabetes; 50 to 100 grams of butter fat when administered to a diabetic may raise his urinary aceton four- to eightfold.[4]

Magnus-Levy[5] gave 11.7 grams of β-oxybutyric acid to a normal dog. This was completely burned. He then gave 11.5 grams to a phlorhizinized dog, with the result that there was an increased elimination of 7.6 grams of β-oxybutyric acid and aceton. Since some aceton was eliminated in the breath, it is evident that the animal had largely lost the power to burn ingested β-oxybutyric acid.

The evidence concerning the formation of the aceton bodies from fat and from some amino-acids has already been discussed (see p.

[1] Magnus-Levy, A.: Ergeb. d. inn. Med., 1908, **1**, 374.
[2] Stadelmann, E.: "Experimentelle-klinische Untersuchungen," Stuttgart, 1890.
[3] Magnus-Levy, A.: Ergeb. d. inn. Med., 1908, **1**, 384.
[4] Fejes, L.: Magyar orvosi Archivum, 1907, **8**, 335.
[5] Magnus-Levy, A.: Ergeb. d. inn. Med., 1908, **1**, 372.

219). It suffices here to recall that Otto Neubauer[1] found that the ingestion of either β-oxybutyric acid or aceto-acetic acid by a diabetic patient always caused the partial excretion of the one given in the form of the other. The reaction is reversible:

$$CH_3.CHOH.CH_2.COOH + O \rightleftarrows CH_3.CO.CH_2.COOH + H_2O$$

In marked acidosis Neubauer found that β-oxybutyric acid amounted to between 60 and 80 per cent. of the total urinary aceton bodies.

If a surviving liver be perfused with blood containing β-oxybutyric acid, the latter is in part converted into aceto-acetic acid.[2] Minced liver or even the aqueous extract of liver tissue will effect the same reaction.[3]

Fischler and Kossow[4] report that the formation of aceton bodies in a phlorhizinized dog is decreased in the presence of an Eck fistula, whereas if a "reversed" Eck fistula be created by diverting the blood from the vena cava into the portal vein, the excretion of aceton bodies is increased fivefold. This points to the liver as the main source of the aceton bodies, if one may accept conclusions drawn from experimental conditions so profoundly abnormal.

The quantity of the aceton bodies in the blood is given by Marriott[5] as follows:

	In 100 C.C. of Blood	
	Aceto-acetic Acid and Aceton	β-oxybutyric Acid
	Milligrams	Milligrams
Normal dog	0.04	3.2
	0.08	1.7
	0.06	1.7
Normal child	0.06	4.4
	0.08	4.4
Phlorhizinized dog	7.2	10.4
Diabetic child in coma	23.4	24.8

The increase in the aceton bodies in the blood is greatest in diabetes mellitus in man, is not so marked in phlorhizin glycosuria in dogs, and is least of all present in depancreatized dogs. Sassa[6]

[1] Neubauer, O.: Verhandl. d. deut. Cong. inn. Med., 1910, **27**, 566.
[2] Embden, G., and Engel, H.: Hofmeister's Beitr. chem. Physiol. u. Path., 1908, **11**, 323.
[3] Wakeman, A. J., and Dakin, H. D.: J. Biol. Chem., 1909, **6**, 373.
[4] Fischler, F., and Kossow, H.: Deut. Arch. klin. Med., 1913, **111**, 479.
[5] Marriott, W. M.: J. Biol. Chem., 1913–14, **16**, 293.
[6] Sassa, R.: Biochem. Z., 1913–14, **59**, 362.

states that the organs of diabetic men dying in coma may contain eight times the normal quantity of β-oxybutyric acid, the liver showing relatively the greatest storage of the substance. In one instance (Case II) 130 milligrams of β-oxybutyric acid were found in 100 grams of the body tissue of a man weighing 70 kilograms, and the author computes the presence of 85 grams of the substance within the body. Marriott's[1] highest figures for 100 c.c. of diabetic blood in man are 28 milligrams of aceto-acetic acid and 45 milligrams of β-oxybutyric acid.

The demonstration by Ringer[2] that propionic acid was completely converted into glucose and that higher fatty acids with *uneven* numbers of carbon atoms yielded glucose in so far as they might form propionic acid by β-oxidation, presents the theoretic possibility of giving to diabetics fats containing these fatty acids, which would yield innocuous glucose instead of acid bodies as the end-products of oxidation. Practical difficulties in the preparation of such fats have alone prevented success in their administration to diabetic subjects.

The result of the formation of acid bodies in the organism leads to a condition of *acidosis*, the alkali reserves being called upon. Not only does ammonia increase in the urine, but there may be a marked fall in the carbon dioxid content of the blood due to a diminution in the quantity of bicarbonate of soda. Magnus-Levy[3] reports an extreme case in which 100 c.c. of the blood of a diabetic just before death in coma contained only 3.3 c.c. of carbon dioxid instead of 40 c.c. normally present.

The reduction in the carbon dioxid combining power of the blood and the consequent lowering of the carbon dioxid tension in the alveoli do not appear in the earlier days of acidosis, provided the acids formed be neutralized with ammonia.[4] The withdrawal of alkali occurs later. Rona and Wilenko[5] find that, despite the acidosis, the hydrogen ion concentration of the blood may remain normal on account of the compensation brought about through the removal of carbon dioxid by the lungs and of acids through the urine. Notwithstanding this control over the blood, the authors believe it possible that there may be a local increase of the hydrogen ion concentration in certain cells and tissues.

[1] Marriott, W. M.: J. Biol. Chem., 1914, **18**, 507.
[2] Ringer, A. I.: *Ibid.*, 1912, **12**, 511.
[3] Magnus-Levy, A.: Arch. exp. Path. u. Pharm., 1900–01, **45**, 389.
[4] Münzer, E.: Z. exp. Path. u. Therap., 1914, **16**, 281.
[5] Rona, P., and Wilenko, G. G.: Biochem. Z., 1913–14, **59**, 173.

Concrete cases of blood analyses are offered by Poulton[1] (see p. 264), who reports concerning the blood of 7 diabetic patients. The first 6 possessed a normal blood reaction. One of them (E. S. M.) following the first examination fell into deep coma and twenty-two hours later showed an abnormally high hydrogen ion concentration. E. H., whose blood reaction was similar, was also in deep coma. The first two patients gave no indication of coma, but all the others were drowsy. B. died in coma eighteen hours after the examination of his blood, which had been normal in reaction.

The figures are in part as follows:

Patient	Alveolar CO_2	pH	Sodium Bicarbonate Daily
	Mm.		Grams
E. R.	38.3	−7.33	0
B. K.	22.0	−7.25	45
F. B.	18.6	−7.36	11
M. T.	16.8	−7.36	6
E. S. M.	15.1	−7.33	8
B.	12.1	−7.35	45
E. H.	8.1	−7.19	60
E. S. M.	7.3	−7.18	45

On the basis of work on a diabetic and comatose boy weighing 32 kg., Magnus-Levy[2] makes the following computation of metabolism. He purposely assumes a high requirement of energy for a lad of this size, or 50 to 55 calories per kilogram, which calls for a total of 1600 to 1700 calories. The boy burned 90 grams of protein and perhaps 200 grams of fat:

	Calories
90 grams protein = 369 calories 200 grams fat = 1909 calories	= 2278
Deduct 97.5 grams oxybutyric acid, 443 calories Deduct 50 grams urinary sugar, 185 calories	= 628
Calories available	1650

Here we perceive an extreme case of diabetic metabolism in which half the energy contained in protein is excreted in urinary sugar and 20 per cent. of that contained in fat is eliminated in the unburned β-oxybutyric acid.

This, then, is the worst picture of the perverted metabolism in diabetes. Sugar cannot burn, fat burns only as far as β-oxybutyric acid, and as for protein, a part of its amino-acids is converted into

[1] Poulton, E. P.: J. Physiol., 1915–16, **50**, p. i.
[2] Magnus-Levy, A.: Ergeb. d. inn. Med. 1908, **1**, 385.

sugar and another part into β-oxybutyric acid, neither of which can be burned.

It is notable that the phlorhizinized cancer patient of Stanley Benedict (see p. 633) who had a D:N ratio of 3.66 excreted 37 grams of β-oxybutyric acid and 4 grams of ammonia daily, which shows that the acidosis of diabetes is coincident with a lack of sugar oxidation. In the diabetic C. K. (see p. 677) a fall in the β-oxybutyric acid excretion preceded the break in the D:N ratio (consult p. 353).

THE THEORY OF KETOSIS

It was pointed out in the third edition of this book that the experiments of Zeller (see p. 353) might be interpreted as indicating that ketosis was absent if the metabolic mixture was such that one molecule of fatty acid could be oxidized in the presence of a triose molecule.

Ringer's[1] interpretation of the reaction was that acetaldehyd derived from glucose formed a chemical union with β-hydroxybutyric acid, enabling it to be oxidized. This substance was partly convertible into glucose and was excreted in the urine if the reaction occurred in the diabetic dog. Woodyatt[2] denied the validity of Ringer's interpretation on the ground that acetaldehyd, like other anesthetics, drives glycogen out of the liver and he stated that this caused the extra glucose elimination in Ringer's dogs. Ringer[3] refuses to accept the criticism of Woodyatt and states that in the phlorhizinized dogs, deglycogenized by epinephrin which were used by Woodyatt, glycogen derived from the reaction between acetaldehyd and β-hydroxybutyric acid is retained in the liver and is not eliminated in the urine. This point needs further clarification.

Woodyatt[4] in 1916 used the following graphic language, "When the mixture of metabolites oxidizing in the body contains more than three molecules of higher fatty acid to one of glucose, then the body 'smokes' with acidosis compounds like an automobile with too much oil in the cylinders."

Newburgh[5] was the first to dare to administer a diet high in fat, low in protein and low in carbohydrate, and to discover the benefits of

[1] Ringer, A. I., and Frankel, E. M.: J. Biol. Chem., 1913–14, **16**, 563.
[2] Sansum, W. D., and Woodyatt, R. T.: *Ibid.*, 1915, **21**, 1.
[3] Ringer, A. I., Dubin, H., and Frankel, F. H.: Proc. Soc. Exper. Biol. and Med., 1921–22, **19**, 92.
[4] Woodyatt, R. T.: J. Am. Med. Assn., 1916, **66**, 1910.
[5] Newburgh, L. H., and Marsh, P. L.: Arch. Int. Med., 1920, **26**, 647.

this diet. Thus Marsh and Waller,[1] in Newburgh's clinic, applied such a diet to a farmer who had severe diabetes. The initial diet was one which involved partial starvation of the patient and contained protein, 20 gm., fat, 85 gm., carbohydrate, 14 gm., and 900 calories. On the 4th day the urine was free from sugar and on the 9th day free from ketones; on the 16th day the blood sugar was normal. The diet was then gradually increased until it contained protein, 43 gm.; fat, 230 gm.; carbohydrate, 25 gm.; and 2350 calories. The fat in the blood originally was 9 per cent. and fell slowly to 6.5 per cent. during 25 days, then more rapidly for 10 days to 3 per cent., and again more slowly until on the 65th day it was 2 per cent. at a time when 230 gm. of fat were being ingested. The fall in blood fat became most marked when the calories in the food became sufficient and nitrogen balance was established. A diet rich in fat does not therefore necessarily produce lipemia.

Newburgh and Marsh[2] describe how every diabetic patient admitted to the wards of the hospital at Ann Arbor receives the initial diet (900 calories) mentioned above. Such a diet produced the same fall in basal metabolism as the then prevalent Allen fasting treatment did, was more rapid in eliminating sugar, and was far less dangerous than fasting. They state (in 1923) that a low protein, low carbohydrate, high fat maintenance diet, given to a large group of diabetic patients since March 1, 1918, maintained in them an aglycosuric state, was not attended by acidosis, maintained nitrogen balance, did not cause hyperlipoidemia (and was attended by its disappearance in those patients in whom it was present at entrance), supplied sufficient energy both to avoid the evils of undernutrition and to permit of an amount of activity compatible with earning a livelihood, and was attended by a downward progress of the disease in uncomplicated cases.

Petrén, at Lund, independently of Newburgh, introduced a similar treatment about the same time and presented this viewpoint before European audiences (see p. 364).

In 1921 Woodyatt[3] wrote a masterpiece upon the subject of diet adjustment in diabetes. He estimated the yields of carbohydrate and fatty acid from the energy yielding staples as follows:

[1] Marsh, P. L., and Waller, H. G.: Arch. Int. Med., 1923, **31**, 63.
[2] Newburgh, L. H., and Marsh, P. L.: *Ibid.*, p. 455.
[3] Woodyatt, R. T.: *Ibid.*, 1921, **28**, 125.

	Glucose Gm.	Fatty Acid Gm.
100 gm. carbohydrate (C) yield in the body	100	0
100 " protein (P) " " " "	58	46
100 " fat (F) " " " "	10	90

Total glucose $= C + 0.58P + 0.1F.$
Total fatty acid $= 0.46P + 0.9F.$

These figures merely represent the fact that in metabolism protein yields 58 per cent. of glucose and 46 per cent. of fatty acid, and fat 10 per cent. of glycerol and 90 per cent. of fatty acid. Woodyatt calculated that there must be at least 1 gm. of glucose available for the proper oxidation of 1.5 gm. of fatty acid, a $\frac{FA}{G}$ ratio of 1.5. Since the molecular weight of glucose is 180 and the average of the molecular weights of palmitic and oleic acids is 270, the relationship between the weights, molecule for molecule, is 1.5. A diet which gave excellent results was made up as follows:

	Gm.	G Gm.	FA Gm.	
C	51	51		
P	70	41	32	
F	125	12	113	
		104	145	$\frac{FA}{G} = 1.4$

To a diabetic, weak, languid, and emaciated, who had not been improved by fasting or by various diets, was finally given a diet of rice and butter (P = 2.5 gm.; C = 24 gm.; F = 102 gm.; 1024 cals.) and this was later increased and eggs added (P = 25 gm.; C = 84 gm.; F = 174 gm.; 2000 cals; $\frac{FA}{G} = 1.6$). With these diets excellent results were achieved which interpreted the good influence of the Newburgh regimen.

The success of the diet explains the secret of von Noorden's "oatmeal cure," in which oatmeal with much fat was administered, and similar "cures" with rice or with potato which have had their vogue.

Simultaneous with the work of Woodyatt was that of Shaffer.[1] Shaffer calculated the number of millimols of glucose and of fatty acid in a given array of food or metabolism products. This gave a method for estimating the relative number of ketogenic and ketolytic molecules present in the metabolizing mixture. A millimol is

[1] Shaffer, P. A.: J. Biol. Chem., 1921, **49**, 143.

equal to one-thousandth of the molecular weight of the substance in grams. Thus:

One gram of glucose $= \frac{1000}{180} = 5.56$ millimols glucose.

One gram of fat $= \frac{1000}{874} \times 3 = 3.43$ millimols fatty acid.

One gram of fat $= \frac{1000}{874} \times \frac{1}{2} = 0.57$ millimol glucose.

One gram of protein N = 3.6 gm. glucose $= \frac{3.6}{180} \times 1000 =$ 20 millimols glucose.

One gram of protein N (from leucin, tyrosin, etc.) = 15 millimols fatty acid.

From calculations in the literature Shaffer found that when there is a molecular ratio between glucose or glucose formers and fatty acid of 1:1, a respiratory quotient of 0.76 prevails and no aceton bodies appear in the urine.

From the story of Benedict's fasting man, given on p. 100, Shaffer calculated that the metabolism of 142 gm. of fat, 42 gm. of glycogen, and the protein equivalent of 8.4 gm. of urinary nitrogen, observed on the 2d day, represented the production of 613 ketogenic millimols and 482 ketolytic[1] (glucose) millimols. Of ketogenic millimols there were 1.27 to 1 of glucose. The respiratory quotient was 0.75 and ketone bodies were in the urine. On the 1st day of fasting the respiratory quotient was 0.78, the metabolic mixture contained 585.6 ketogenic millimols and 602 ketolytic millimols or 0.94 of fatty acid (ketogenic) to 1 of glucose (ketolytic) and no ketone bodies appeared in the urine.

From an original agreement with Woodyatt that an equimolecular ratio should exist between glucose and fatty acid if ketosis is to be avoided, Shaffer[2] later concluded that if the ketone bodies were present in large excess, then one triose molecule only was needed for the combustion of a molecule of fatty acid.

Thus, in a balanced equation according to his older method of computation, he found in the case of the diabetic man C. K. (see p. 677) that if the relation were 1:1, then in an 8-day period 559 gm. β-hydroxybutyric acid were to be expected against 444 gm. actually

[1] At the suggestion of S. R. Benedict, *ketolytic* is used for *antiketogenic*.
[2] Shaffer, P. A.: J. Biol. Chem., 1922, **54**, 399.

found. However, if one triose molecule were oxidized in association with one of fatty acid, then 436 gm. of β-hydroxybutyric acid should have arisen, and this latter figure tallies with the quantity found.

This result is in full accord with the calculations of Wilder and Winter[1] with regard to the patient mentioned on p. 656, but, although these authors believe that one molecule of glucose may be ketolytic to two molecules of aceto-acetic acid, they advise that in preparing a diet this ratio should be avoided by a safe margin.

It is not reasonable to believe that if the theoretical minimum of glucose be ingested it is at all times so distributed in all organs of the body that one mol will be available whenever and wherever two mols of fatty acid are destroyed.

In a carefully executed piece of work regarding diet adjustment for the diabetic patient McCann and his associates[2] conclude that ketonuria ceases sharply when Woodyatt's $\frac{FA}{G}$ ratio reaches 1.5, which corresponds to a molecular ratio of 1:1. This refers, of course, to the actual oxidation of metabolites in the body. Parenthetically it may be stated that those interested in the behavior of glycerol, hexose-phosphate, and glycurophosphate in diabetes will find information in this article by McCann.

Papers 33, 34, and 37 on "Clinical Calorimetry" from the Russell Sage Institute of Pathology were devoted to the subject of ketosis and the respiratory exchange in diabetes. Richardson and Mason[3] placed patients with mild or moderately severe diabetes in the respiration calorimeter and determined the materials they oxidized at least 12 hours after the last meal. These patients then received a "replacement diet" every 2 hours which contained the exact amount of protein, fat, and carbohydrate which it was calculated they had oxidized during a 2-hour determination of the basal metabolism. In one case the ingestion of the diet increased the heat production 5.1 per cent., in another instance lowered it 1.7 per cent. The average total increase was only 2.6 per cent. for the whole series. Actually a replacement diet given in small amounts at frequent intervals holds the metabolism essentially at the level reached by fasting. The tendency of the replacement diet was (1) to increase the total protein

[1] Wilder, R. M., and Winter, M. D.: J. Biol. Chem., 1922, **52**, 393.
[2] McCann, W. S., Hannon, R. R., Perlzweig, W. A., and Tompkins, E. H.: Arch Int. Med., 1923, **32**, 226.
[3] Richardson, H. B., and Mason, E. H.: J. Biol. Chem., 1923, **57**, 587.

metabolism, (2) to increase the oxidation of carbohydrate, and (3) to store the ingested fat. The authors say, "The tissues of these undernourished diabetics seem to soak up fat like a sponge." One of them oxidized only 37 gm. of 91 gm. given in the food. When extra fat was added to the replacement diet it was deposited in the body without materially raising the heat production.

Richardson and Ladd,[1] after many experiments with patients in the calorimeter, conclude that the threshold of ketosis is at the level of 1.5 gm. of fatty acid to 1 of glucose, as stated by Woodyatt, and suggest that interpretations based on the fatty acid: glucose ratio of a diet *ingested* may be marred by the quite different relation of the two factors in their oxidation in the body. This they offer in explanation of statements that ketosis is prevented at a relatively lower level of sugar oxidation.

Another paper is by Richardson and Levine,[2] who show that in diabetics suffering from infection the higher degree of acidosis is due to the fact that the infection reduces their power to oxidize glucose. For the quantity of aceton bodies excreted for a given fatty acid: glucose ratio is the same in both infected and non-infected individuals.

The most recent paper on this subject is by Mason,[3] who tested the ketogenic-ketolytic ratio is obesity during periods of reduction in body weight. In four of five individuals in whom the

$$\frac{\text{Ketogenic mols}}{\text{Ketolytic mols}}$$

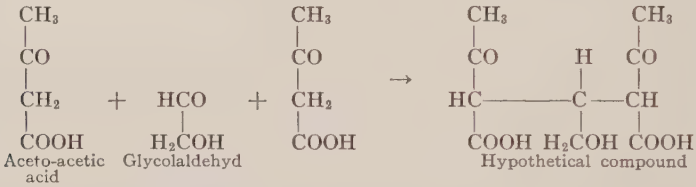
in the metabolizing mixture was between 1.5 and 2 there was no acidosis observed during periods covering between 63 and 117 days. This means that one triose molecule suffices for the normal oxidation of one of fatty acid. In the person having the greatest weight (173 kg.), during a period of 70 days, the molecular ratio varied between 2.38 and 2.72 and there was no acidosis. Only 6.9 per cent. of the calories arose from protein, 2.5 per cent. from carbohydrate, and 90.6 per cent. from fat, and this without any acidosis. Is this an isolated anomaly? A hog may ingest butter in quantity with or without added butyric acid as its sole nutriment and develop little or no acidosis;[4] dogs and rats are very resistant to the development of acidosis, but Friedemann[5] states that a capuchin monkey develops acute fasting

[1] Richardson, H. B., and Ladd, W. S.: J. Biol. Chem., 1923–24, **58**, 931.
[2] Richardson, H. B., and Levine, S. Z.: *Ibid.*, 1925, **63**, 465.
[3] Mason, E. H.: J. Clin. Invest., 1927, **4**, 93.
[4] Lueg, W. and Flaschenträger, B.: Klin. Wchnschr. 1925, **4**, 694.
[5] Friedemann, T. E.: Proc. Soc. Exper. Biol. and Med., 1926, **24**, 223.

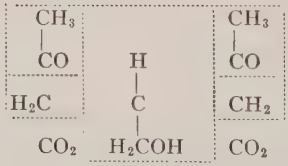
ketosis which disappears on giving carbohydrates, in full accord with the rules of Shaffer's ketogenic-ketolytic balance. The question presents itself whether, as regards the human being, we are dealing in matters of this kind with a law or with a constitutional variable.

In Vitro Ketolytic Reactions.—Shaffer[1] discovered that if he added peroxide of hydrogen to an alkaline solution of aceto-acetic acid there was only a very slight oxidation of the substance after 24 hours. If, however, he added glucose, a rapid and complete oxidation of the acid occurred within one hour. Also, after addition of fructose, glycerol, or glycolaldehyd, aceto-acetic acid was destroyed. However, addition of lactic acid or acetaldehyd had no influence upon the ketolytic reaction. In neutral or acid solutions there was no oxidation of glucose or aceto-acetic acid.

Shaffer and Friedemann[2] have suggested as a possible biological reaction between aceto-acetic acid and glycolaldehyd and the following formula:



The hypothetical compound would presumably lose 2 molecules of CO_2 and become oxidized with the production of 2 molecules of acetic acid, 2 of formic acid, and 1 of glycollic acid, as appears below:



Other reactions have been suggested.[3]

According to the above one diose molecule only is required for the oxidation of two molecules of aceto-acetic acid. And indeed Friedemann[4] has shown that under optimum conditions, in an alkaline solution containing two molecules of aceto-acetic acid, they are

[1] Shaffer, P. A.: J. Biol. Chem., 1921, **47,** 433.
[2] Shaffer, P. A., and Friedemann, T. E.: *Ibid.*, 1924, **61,** 585.
[3] West, E. S.: *Ibid.*, 1925, **66,** 63; 1927, **74,** p. xlii.
[4] Friedemann, T. E.: *Ibid.*, 1925, **63,** p. xxi.

completely oxidized in the presence of one molecule of glucose, of fructose, of mannose, or of glycolaldehyd.

Friedemann further states that glucosone, $CH_2OH(CHOH)_3$—CO—CHO, which may be a first oxidation product of glucose, is ketolytic in neutral or slightly alkaline solutions, even when no H_2O_2 is present.

Objection has been made to the interpretations of Shaffer's work, that the strength of the alkali used was far greater than that which exists in physiological reactions. Notwithstanding this, the work is highly suggestive and stimulating.

BLOOD FAT

B. Fischer[1] reported a case of coma diabeticum in which the blood-serum contained 23 per cent. of fat. Klemperer and Umber[2] state that of 9 diabetics with acidosis 7 had lipemia. Adler[3] and Imrie[4] report cases in which the blood-serum contained respectively 29 and 14 per cent. of fat plus cholesterol; of the latter there were 3.1 and 1.5 per cent. in the serum in the 2 cases. Lecithin was absent, and Imrie found that the fatty acids entering into the composition of the blood fat had an iodin number similar to that of the fatty acids entering into the composition of subcutaneous fat. Hence, the lipemia was due to the mobilization of tissue fat.

Bloor[5] has reported upon the blood of a diabetic which contained 13 per cent. of fat. The total lipoid was 20 times, lecithin 5 times, and cholesterol 9 times the normal value. The greatest increase, therefore, was in the amount of true fat. If lipemia subsides, fat diminishes first and cholesterol last.

Rabinowitch[6] states that a normal cholesterol value in the blood plasma indicates that the diabetic patient is in good condition.

SPECIAL CALCULATIONS USED FOR MEASURING THE RESPIRATORY METABOLISM

Turning the attention now to the character of the *total metabolism*, one finds that the severely diabetic patient lives at the expense of protein and fat, both of which are incompletely oxidized by his

[1] Fischer, B.: Virchow's Arch. path. Anat., 1903, **172,** 30 and 218.
[2] Klemperer, G., and Umber, H.: Z. klin. Med., 1908, **65,** 340.
[3] Adler, M.: Berliner klin. Wchnschr., 1909, **46,** 1453.
[4] Imrie, C. G.: J. Biol. Chem., 1915, **20,** 87.
[5] Bloor, W. R.: *Ibid.*, 1921, **49,** 201.
[6] Rabinowitch, I. M.: Canadian Med. Assn. J., 1927, **17,** 171.

organism. It follows that the ordinary methods of computation of the respiratory quotients and of the heat value of the protein and fat metabolism must be scrutinized.

Magnus-Levy[1] was the first to make calculations of this sort. Lusk[2] has reviewed the subject and has published a calculation for the value of the respiratory quotient of protein when the urinary D:N ratio is 3.65:

	O_2 Grams	CO_2 Grams
Normal oxidation of 100 grams beef protein	138.18	152.17
Deduction for 16.28 gm. × 3.65 which corresponds to 59.41 gm. glucose	63.38	87.15
	74.80	65.02

Converting the ratio of weights into the ratio of volumes one finds that the diabetic R. Q. for protein is 0.632.

The following calculation shows the caloric value to the organism of 1 gram of urinary nitrogen in diabetes when the D:N is 3.65:

	Calories
Normal value of 1 gm. urinary N	26.51
Deduct glucose 3.65 × 3.755	13.71
Value of 1 gm. urinary N in diabetes	12.80

If large amounts of ammonia are eliminated without being synthesized to urea—which is produced by an endothermic reaction—1 calorie per gram of such extra ammonia nitrogen may be added to the calculated heat production.

If one uses the modified figures to calculate the "non-protein respiratory quotient" in severe diabetes, it is found that the combustion of fat is indicated. A few illustrative calculations are given below, taken from the work of Lusk and of Allen and DuBois:

	D:N	R. Q.	Non-protein R. Q.
Phlorhizinized dog	3.54	0.687	0.704
Diabetic man (G. S.)	3.5	0.697	0.700
Diabetic man (C. K.)	3.97	0.687	0.699

The last subject eliminated 71 grams of β-oxybutyric acid on the day of the experiment. It is evident that when allowance is made in the calculations for the altered course of the metabolism of protein in diabetes, the remainder of oxidizable substance possesses approximately the respiratory quotient of fat, which is 0.707.

Theoretically speaking, the subject is more complicated. For example, if ammonia be used to neutralize β-oxybutyric acid, the

[1] Magnus-Levy, A.: Arch. f. Physiol., 1904, 379.
[2] Lusk, G.: Arch. Int. Med., 1915, **15**, 939.

carbon dioxid with which it would have united to form urea will be eliminated in the respiration and tend to raise the respiratory quotient.

Magnus-Levy has called attention to a possible reduction in the respiratory quotient when β-oxybutyric acid is formed from fat. He estimates that the maximal quantity of β-oxybutyric acid derivable from 100 grams of fat is 36 grams. Under these circumstances, the respiratory quotient for fat would be reduced from 0.707 to 0.669. The case is not so simple, however, for if the 36 grams of acid formed neutralized sodium bicarbonate, 15.23 grams of carbon dioxid would be eliminated.

These relations are shown in the following table:

THEORETIC RESPIRATORY QUOTIENT WITH β-OXYBUTYRIC ACID FORMED FROM FAT

	Oxygen, Liters	Carbon Dioxid, Liters	R. Q.
100 gm. fat	201.9	142.73	0.707
36 gm. β-oxybutyric acid	34.85	30.96	0.889
	167.05	111.77	0.669
Add for 15.23 gm. CO_2 from $NaHCO_3$		7.74	
Possible end-result	167.05	119.51	0.715

Since other bases than sodium bicarbonate may be used for the neutralization of β-oxybutyric acid, it is apparent that the exact determination of the theoretic respiratory quotient when this acid is produced in large amounts in human diabetes is at present impossible.

The establishment of the diabetic quotient at the level of 0.69 also throws light on the dogma regarding the conversion of fat into sugar. Pembrey[1] calculated that if olein were in large part converted into glucose the respiratory quotient for the reaction would be 0.281. The actual findings of the respiration measurements carry the refutation of the idea that fat may be converted into sugar.

If fatty acid passes into glucose, then one may write the transformation as follows:

$$\underset{\text{Palmitic acid}}{3C_{16}H_{32}O_2} + 21O_2 = \underset{\text{Glucose}}{8C_6H_{12}O_6}$$

To produce 1 gm. of glucose from fatty acid by this reaction requires 0.465 gm. or 0.326 liters of inspired oxygen. The greater the extent of this reaction, the lower the respiratory quotient will fall. In our laboratory, however, we have come to regard a fasting diabetic

[1] Pembrey, M. S.: J. Physiol., 1901–02, **27**, 71.

dog, with its constant respiratory quotient of 0.69 to 0.70, as a very good test of the accuracy of the respiration determinations made with the apparatus. Lower quotients lead us to expect, and to find, leaks in the box instead of forcing the conclusion that fat is passing over into sugar.

It may be well to insert a warning against the too literal interpretation of respiratory quotients obtained under grossly abnormal circumstances. This may be illustrated by the experiments of Porges and Salomon,[1] who ligated the abdominal aorta and the inferior vena cava just below the diaphragm in depancreatized dogs, thereby cutting off the blood supply to the abdominal organs and probably eliminating half the normal quantity of blood from the circulation. Under these circumstances the respiratory quotient rose to unity and the authors concluded that the diabetic organism could oxidize glucose. This doctrine was refuted by Murlin, Edelmann, and Kramer,[2] who showed that the high respiratory quotient was merely incident to the elimination of carbon dioxid from the blood itself.

One by one the bulwarks of the doctrine of the conversion of fat into glucose have been shattered, and it may now be relegated to the realm of scientific superstition.

THE RESPIRATORY METABOLISM IN SEVERE DIABETES

Among the earliest investigations of Pettenkofer and Voit[3] was a respiration experiment on a diabetic individual. The authors compared the metabolism of a diabetic with that of a normal man, as indicated in the following table:

COMPARISON OF A NORMAL AND A DIABETIC MAN

	Grams in the Food	Grams Burned in the Body
Healthy man, Protein	120	120
" " Fat	112	83
" " Sugar	344	344
Diabetic man, Protein	107	158
" " Fat	108	158
" " Sugar	337	0

(337 grams of sugar in the urine.)

It is seen here that the fat and protein metabolism are increased in order to compensate for the non-combustion of the sugar. Several years later, on the basis of these experiments, E. Voit calculated that

[1] Porges, O., and Salomon, H.: Biochem. Z., 1910, **27**, 143.
[2] Murlin, J. R., Edelmann, L., and Kramer, B.: J. Biol. Chem., 1913–14, **16**, 79.
[3] Pettenkofer, M., and Voit, C.: Z. f. Biol., 1867, **3**, 380.

a diabetic on a moderate mixed diet yielded 1015 calories per square meter of surface, while the normal individual of similar build produced 1020 calories.

The diabetic condition, therefore, does not involve a decrease in the quantity of energy produced, but only an alteration in the source of the energy.

In 1910 DuBois and Veeder[1] published experiments accomplished with a Pettenkofer-Voit respiration apparatus in Kraus's clinic at Berlin, which showed that a diabetic patient produced 5 per cent. more heat than a normal man of the same size, the food intake and the amount of muscular activity being the same in both.

Rubner[2] found the metabolism of a fasting dog was the equivalent of 477.8 calories per day, which rose to 510.4 calories after the administration of phlorhizin, an increase of 7 per cent. This increase Rubner rightly attributed to the specific dynamic action of the increased protein metabolism. Lusk[3] has reported an increase in the heat production of 70 per cent. after administering phlorhizin to a dog.

The same influences are active in the depancreatized dog, the heat production being increased 42 per cent., according to Falta, Grote and Staehelin, and Murlin and Kramer.[4]

In the phlorhizinized man of Stanley Benedict (see p. 662) the protein metabolism did not increase as happens in other species, and it is therefore open to question whether there was any increase in his total energy production.

The question of the total energy production in the human diabetic has been extensively studied by Benedict and Joslin[5] and by Allen and DuBois.[6] Whatever of criticism may be found in the following lines, it is to be borne in mind that there was never any question of the absolute accuracy of all of this work; the criticism regards only the interpretation. Pflüger has truly stated that criticism is the mainspring of every advance and the Altmeister added, "deshalb übe ich es." It will be seen that the criticism ended in harmony of opinion.

[1] DuBois, E. F., and Veeder, B. S.: Arch. Int. Med., 1910, **5**, 37.
[2] Rubner, M.: "Energiegesetze," 1902, p. 370.
[3] Lusk, G.: J. Biol. Chem., 1915, **20**, 598.
[4] Falta, W., Grote, F., and Staehelin, R.: Hofmeister's Beitr. chem. Physiol. u. Path., 1907, **10**, 199. Murlin, J. R., and Kramer, B.: J. Biol. Chem., 1913, **15**, 380.
[5] Benedict, F. G., and Joslin, E. P.: "Metabolism in Diabetes Mellitus," Carnegie Institution of Washington, Pub. 136, 1910; "Metabolism in Severe Diabetes," *Ibid.*, Pub. 176, 1912.
[6] Allen, F. M., and DuBois, E. F.: Arch. Int. Med., 1916, **17**, 1010.

Lusk[1] criticized the first publication of Benedict and Joslin and computed that the average increase in metabolism was not 15 per cent. above the normal, as was stated, but did not exceed 5 per cent. The second publication of Benedict and Joslin maintained that there was an increase of between 15 and 20 per cent. in patients suffering from diabetes, and attributed the increase to acidosis.

In 1923 Joslin[2] found that the increased metabolism amounted to 12 per cent. of the Harris-Benedict prediction standard.

The establishment of an accurate method of estimating the basal metabolism of normal men through the labors of DuBois has given a method of interpretation of metabolism results which has not heretofore been available. If the height-weight chart of DuBois be used to obtain the surface area and be applied to the diabetic cases and normal controls of Benedict and Joslin ("Severe Diabetes," Table 132), the following calculations may be made:[3]

	Per Cent.
Average variation from normal of 20 controls	−8.6
Average variation from normal of 19 diabetics	+2.0

The increase in metabolism is, therefore, 2 per cent. above the true normal, but 11 per cent. above the normal controls selected by Benedict and Joslin. This selection may have been justified, for in order to choose individuals who were like the diabetic patients, emaciated controls were indicated and such show a subnormal basal metabolism. Allen and DuBois have pointed out that herein lies the fundamental cause of the difference in viewpoint. These authors have published a summary of the carefully investigated cases of diabetes mellitus, 26 in all. They found that the basal metabolisms of one-half of these were within the normal range of ±10 per cent.; 9 cases showed increases of 11 to 23 per cent. above the normal basal. Of these cases which manifested a higher metabolism, 3 had severe, 2 marked, 1 moderate, and 3 little or no acidosis. The patient who showed the greatest rise in metabolism had very slight acidosis. Four patients showed metabolisms of between 14 and 19 per cent. below the normal. Of the 17 patients whose basal metabolisms were normal or below the normal, 8 manifested very severe acidosis. The conclusion follows that acidosis cannot be the immediate cause of the increased metabolism when this is found in diabetes.

[1] Lusk, G.: "Science," 1911, **33**, 434.
[2] Joslin, E. P.: Carnegie Institution of Washington, Pub. 323, 1923.
[3] Allen, F. M., and DuBois, E. F.: *Loc. cit.*

In their analysis Allen and DuBois considered for the first time the factor of emaciation. They call attention to Magnus-Levy's[1] description of a neurasthenic youth who had partially starved himself for a year or more. On entrance to the hospital he was "skin and bones." During the first experimental period he received his former dietary containing 700 to 800 calories daily and then received abundant food.

Date	Weight in Kg.	Calories per Hour	Calories per Sq. M. per Hour	Relationship of Metabolism to Average Normal of 39.7	Remarks
Nov. 16 to 21.....	36.2	34.8	26.6	−33%	Low diet.
Nov. 23 to Dec. 9....	38.0	44.9	33.0	−17%	Liberal diet.
Nov. 13 to May 8....	52.2	61.9	40.5	+ 2%	Liberal diet.

These valuable data indicate that if a man whose metabolism is normal has been reduced in weight by 30 per cent., his metabolism when he is fed with a low dietary may be reduced 44 per cent. below the actual normal level, or 33 per cent. below, as measured by the normal per square meter of surface (see p. 173.) If a liberal diet be given at this juncture, the total heat production is 26 per cent. below the actual normal, or 17 per cent. below if recorded on the basis of surface area. This leads to the query whether the basal metabolism of the emaciated diabetic is not really below that of a normal man.

Among the cases cited by Allen and DuBois there are 6 who show an emaciation of over 20 per cent., as follows:

Case	Urinary N per Day, Grams	Per Cent. Loss from Greatest Body Weight	Per Cent. Variation from Normal Calories per Sq. M.
I.....	14	30	+14*
T.....	9–12	28	0
V.....	7– 9.5	26	+15
C. K.....	20	27	+ 3
G. S.....	11–15	31	− 5
W. G.....	14–20	42	−15
Average.....	.....	..	+ 3

* Nervous individual.

It is evident that if the metabolism of a normal man, who through emaciation has lost 30 per cent. of his body weight, is 33 per cent. (or

[1] Magnus-Levy, A.: Z. klin. Med., 1906, **60**, 177.

when well nourished 17 per cent.) below the normal level of metabolism, then the emaciated diabetic has in reality a higher heat production than he would have had if he had been free from diabetes. This is emphatically shown in the case of C. K., soon to be more fully described. This individual, who had diabetes in a severe form, subsequently became entirely free from sugar and manifested a high degree of tolerance for carbohydrate. The metabolism of the different periods may thus be summarized:

Condition	Weight	Urine	R. Q.	Per Cent. Loss from Greatest Body Weight	Per Cent. Variation from Normal Calories per Square Meter of Surface
	Kg.	N Gm.			
C. K.: Severe diabetes...	56.7	36.4	0.687	27	+15
Severe diabetes...	56.5	20.0	0.707	27	+ 3
Recovery.....	45.8	....	0.92	43	−36

It is evident that in this emaciated individual the metabolism would have been lower in the first instance had he not been diabetic. The high protein metabolism would sufficiently account for the increased total heat production in this patient, although in some other instances of increased metabolism in diabetes this factor does not apparently always suffice to explain the increase. The frequent presence of lipemia (see p. 311) may explain in part the increased metabolism. The onset of diabetes in this case was very rapid. Nowhere in the literature is the protein metabolism in diabetes mentioned as being so high, and in no other case are the results of metabolism experiments so nearly akin to those obtained in experimental animals.

A preliminary report of the patient C. K. of Geyelin and DuBois[1] gives details of his metabolism in a table which is reproduced on page 677.

On the fifth day of a preliminary fast the D:N ratio was 2.95. Then for four days he was given a mixed diet. After this followed a diet containing about 100 grams of protein and the D:N rose to 3.97, 4.01, and 3.87 on three successive days, the blood sugar probably falling. On the first of these days there was distinct drowsiness; there were 36.4 grams of nitrogen in the urine after an intake of 19 grams

[1] Geyelin, H. R., and DuBois, E. F.: J. Am. Med. Assn., 1916, 66, 1532.

CLINICAL AND EXPERIMENTAL DATA IN CASE OF C. K.

Date	Food Intake, Gm.			Output, Glucose, Gm.	Urine, N, Gm.	D:N Ratio	Beta-oxybutyric Acid, Gm.	Blood CO_2, Mm. Hg.	Blood Sugar, Per Cent.	Average R. Q.	Average Non-protein R. Q.	Average Calories per Hour	Average Calories per Sq. M. per Hour, Linear Formula[1]	Weight, Kg.
	Carbohydrates	Protein	Fat											
1915														
Dec. 8–9	0	0	0	74.9	27.9	2.68	43.7	30.4	0.313					57.4
Dec. 9–10	0	0	0	78.3	29.8	2.61	34.6	.....	.....	.....	.....	.....	.....	57.8
Dec. 10–11	0	0	0	74.2	24.8	2.95	.....	26.6	0.340	.....	.....	.....	.....	58.2
Dec. 11–12	41.5	17.5	17.7	108.0	30.6	2.17	60.0	21.1	0.312	.....	.....	.....	.....	56.7
Dec. 12–13	50.	50.1	69.6	112.0	34.5	1.8	53.0	22.7	.....	.....	.....	.....	.....	57.0
Dec. 13–14[2]	50.	55.2	58.5	118.7	35.4	1.92	57.9	22.5	.....	.....	.....	.....	.....	57.2
Dec. 14–15	53.3	58.	51.2	118.5	37.73	1.73	55.2	.....	.....	.....	.....	.....	.....	56.7
Dec. 15–16	23.5	118.6	41.0	167.9	36.37	3.97	70.8	19.95	.....	0.687	0.699	81.86	45.7^3	56.7
Dec. 16–17	0.4	99.	5.6	153.4	38.27	4.01	75.1	19.6	.....	0.714	0.743	76.43	42.6^3	56.8
Dec. 17–18	0.4	39.4	2.9	140.29	36.29	3.87	87.38	35.4	.....	.....	.....	.....	.....	57.9
Dec. 18–19	0	0	0	55.14	20.01	2.76	58.52	35.4	0.150	0.707	0.706	73.18	40.8	56.5
Dec. 19–20	0	0	0	44.25	16.72	2.65	56.84	49.7	.....	.....	.....	.....	.....	57.2
Dec. 20–21	1.0	10.	0	35.34	14.07	2.44	41.17	52.5	0.177	0.721	0.718	66.33	37.0	56.9
Dec. 21–22	1.6	20.	0	39.73	14.4	2.65	26.21	.....	0.170	.....	.....	.....	.....	56.6
Dec. 22–23	5.6	21.	0.1	25.97	18.25	1.12	10.95	52.8	0.181	0.734	0.728	62.82	35.9	54.3
Dec. 23–24[4]	0	0	0	17.01	10.43	....	.....	46.3	0.206	.....	.....	.....	.....	54.9
Dec. 24–25	0	90.	15.8	15.16	18.32	....	.....	46.2	.....	.....	.....	.....	.....	53.0
Dec. 25–26	0	90.	15.8	32.75	32.70	....	.....	40.9	.....	.....	.....	.....	.....	53.4
Dec. 26–27	0	0	0	10.4	14.28									
Dec. 27–28	0	0	0	0	10.50	....	.....	.....	.....	.....	.....	.....	.....	52 6
Dec. 28–29	0	0	0	0	9.05	.....	0.241	40.95	0.195	.....	.....	.....	.....	52.3
Dec. 29–30	0	51.9	7.9	?	13.79	....	.....	.....	.....	.....	.....	.....	.....	52.6
Dec. 30–31	0	0	0	+	13.72	....	.....	.....	.....	.....	.....	.....	.....	52.3
1916														
Jan. 31–1	0	0	0	0	8.78	....	.....	.....	.....	.....	.....	.....	.....	51.2
Feb. 16[5]	.....	....	....	0	.....	0	0	.....	.....	0.915	0.973	42.96	25.4	45.8
Mar. 8[5]	.....	....	....	0	.....	0	0	.....	.....	0.860	0.872	50.02	29.1	48.3

[1] Average basal normal 39.7 calories per square meter per hour.
[2] Transferred to Bellevue Hospital.
[3] After meals which might cause increase in metabolism of 5 to 10 per cent. above basal.
[4] Returned from Bellevue Hospital.
[5] Transferred to Bellevue Hospital. Liberal diabetic diet the days before these calorimeter observations.

in the food; 71 grams of β-oxybutyric acid were eliminated in the urine or about the quantity which could have arisen from the oxidation of fat during the period; the carbonic acid tension in the blood was one-half the normal, and the respiratory quotient was 0.687. The metabolism presented the picture of complete diabetes (see p. 670). Several who saw the patient pronounced the outlook hopeless. Joslin, who happened to be in New York at the time, gave a favorable prognosis. This prognosis was correct. A period of fasting interrupted by days of very low diets resulted in the complete disappearance of glucose and of high nitrogen elimination in the urine within ten days, and on the eleventh day only 0.2 gram of β-oxybutyric acid was eliminated.

The case of C. K. exemplifies the method of treatment of diabetes known as the "Allen method." Weintraud,[1] in the clinic of Naunyn, was the first to recommend the interpolation of occasional fasting days for the benefit of the diabetic patient, and Naunyn[2] practised the reduction of the body weight of the patient, both by interposing single fasting days and by giving 600 grams of green vegetables which contain little nourishment. Allen, however, on the basis of many fasting experiments with depancreatized dogs,[3] obtained information which he was subsequently able to apply to many diabetic patients[4] in the Rockefeller Hospital. It is certain that he was the first to introduce a rigorous régime of fasting until the diabetic patient becomes free from urinary glucose and from acidosis. Frequently whisky was administered as the only nourishment. Benedict and Török[5] were able to reduce the aceton excretion, as well as that of nitrogen and glucose, after administering alcohol to a diabetic. The experiments of Otto Neubauer[6] showed that red wine reduced the sugar output and the acidosis in diabetes, and Allen and DuBois found indications that the administration of whisky favored the oxidation of glucose in the diabetic. Joslin[7] and Allen and DuBois report that during the clearing up of the diabetes in a fasting patient respiratory quotients are found which are higher than could possibly be obtained from the oxidation of body protein and fat alone. This may possibly

[1] Weintraud, W.: Centralbl. klin. Med., 1893, **14**, 737.
[2] Naunyn, B.: Z. ärzt. Fortbild., 1908, **5**, 737.
[3] Allen, F. M.: "Glycosuria and Diabetes," Boston, 1913.
[4] Allen, F. M.: J. Am. Med. Assn., 1914, **63**, 939; 1916, **66**, 1525.
[5] Benedict, H., and Török, B.: Z. klin. Med., 1906, **60**, 329.
[6] Neubauer, O.: Münchener med. Wchnschr., 1906, **53**, 791.
[7] Joslin, E. P.: Am. J. Med. Sc., 1915, **150**, 485.

be due to the oxidation of the accumulated aceton bodies, the respiratory quotient of β-oxybutyric acid being 0.89, an explanation given by Joslin, who has found respiratory quotients in fasting diabetics as high as 0.8.

Although the great majority of diabetic patients were cured by the fasting treatment, so that they lived on a carefully regulated diet without showing glycosuria, still there were some cases that did not yield to such treatment. Joslin[1] has reported concerning 14 such patients, who were diabetics of long standing, or very severe or complicated cases.

The advent of the Newburgh diet, which has already been described, has resulted in a change in the treatment of diabetic patients, who are now spared the pangs of weakness and hunger.

Bernstein and Falta[2] found that the intravenous injection of glucose into diabetic patients with respiratory quotients of 0.69 does not alter the quotient. Also that the injection of epinephrin, though it increases the output of urinary sugar, does not change the respiratory quotient.

The inability of the complete diabetic to oxidize glucose is also well shown in a patient of Rabinowitch[3] to whom he gave 25 gm. of glucose.

	R. Q.	Blood Sugar Per Cent.
Basal level	0.717	0.210
60 min. after glucose	0.720	0.278
120 min. after glucose	0.712	0.302

If the respiratory quotient is high in diabetes the blood sugar does not rise greatly, for a high respiratory quotient betokens the presence of insulin, leading to the oxidation of glucose and to deposition of glycogen (see p. 651).

One of the most interesting researches upon diabetes ever accomplished is that of Mosenthal and Lewis[4] in Janeway's Baltimore clinic.

The following table shows the results obtained from a fasting diabetic with a D:N ratio closely approximating that found in the phlorhizinized dog, and resembling a phlorhizinized man (see p. 633) both as regards the D:N ratio and in the quantities of ammonia and β-oxybutyric acid eliminated.

[1] Joslin, E. P.: Boston Med. and Surg. J., 1916, **174**, 371 and 425.
[2] Bernstein, S., and Falta, W.: Deut. Arch. klin. Med., 1918, **127**, 1.
[3] Rabinowitch, I. M.: J. Clin. Invest., 1925–26, **2**, 143.
[4] Mosenthal, H. O., and Lewis, D. S.: Johns Hopkins Hospital Bul., 1917, **28**, 187.

DIABETIC PATIENT PRACTICALLY FASTING

(One egg and green vegetables containing 2 to 6 grams carbohydrate per day during last five days. Wh. = whisky; Wi. = wine. Bicarbonate of soda also administered. The D:N is calculated after subtracting ingested carbohydrate.)

Day of Fast	Glucose	Nitrogen	D:N	β-Oxybutyric Acid	$NH_3 - N$	Alveolar CO_2 Tension	Alcoholic Beverage
	Grams	Grams		Grams	Grams	Mm.	C.C.
4	36.9	10.2	3.64	64.9	4.3		
5	40.3	10.8	3.71	66.0	4.5		
6	36.3	9.8	3.46	50.6	4.2	19.5	
7	31.9	9.0	2.89	64.9	3.9	....	40 Wh.
8	35.1	9.6	3.44	78.0	4.4	....	24 Wh.
9	38.0	10.5	3.28	111.2	4.4	....	8 Wh.*
10	34.7	8.9	3.58	106.6	4.0	....	490 Wi.
11	35.7	8.7	3.68	73.0	4.2	24.6	345 Wi.
12							
13	Death.						

* And 360 c.c. wine.

At the beginning of the investigation the blood sugar of the diabetic was 0.33 per cent., but fell on the eighth and ninth days to 0.25 and 0.24 per cent.

Patients of this refractory type may now be treated with insulin.

EFFECT OF MECHANICAL WORK IN DIABETES

Physical weakness is one of the commonest symptoms of diabetes.[1] Richardson and Levine[2] have demonstrated that, whereas in normal people the respiratory quotient increases as the result of muscular work, the quotient declines under like conditions in diabetes. The quantity of glucose oxidized remains the same, and the diabetic accomplishes the work at the expense of an increased oxidation of fat. Compare with the experiment of Grafe and Salomon cited on p. 445.

BRIEF NOTES ON TREATMENT

Von Noorden's oatmeal cure has occupied a prominent place in diabetic therapy. Blum[3] denied its specific efficacy and correctly attributed the results to the low protein dietary (see p. 662). Rolly,[4] on the basis of respiratory experiments, concluded that there was no

[1] Williams, J. R.: Arch. Int. Med., 1917, **20**, 399; Fitz, R., and Murphy, W. P.: *Ibid.*, 1924, **34**, 402; Bowen, B. D., and Carmer, M. E.: J. Clin. Invest., 1925–26, **2**, 299.

[2] Richardson, H. B., and Levine, S. Z.: J. Biol. Chem., 1925, **66**, 161.

[3] Blum, L.: Münchener med. Wchenschr., 1911, **58**, 1433.

[4] Rolly, F.: Deut. Arch. klin. Med., 1912, **105**, 494.

difference in the value of the various forms of starch ingested by the diabetic, and Joslin[1] showed the failure of either oatmeal or potato starch to raise the respiratory quotient in severe diabetes. Baumgarten and Grund[2] have separated the starch and other constituents of oatmeal and have administered them separately to diabetics without improving their condition.

Grafe[3] has advocated the use of caramel in diabetes because of the glucosane therein contained. This substance, when given to phlorhizinized dogs by Deuel, Waddell, and Mandel[4] was not oxidized, was completely eliminated in the urine after intraperitoneal or subcutaneous injection, did not change the D:N ratio nor affect the glycogen reserves. This method offers a way of laboratory analysis of supposed cures for diabetes.

The elimination of β-oxybutyric acid from the system is furthered by the administration of alkalies. Stäubli[5] reports a diabetic who eliminated 34 grams of β-oxybutyric acid daily when the diet contained 60 grams of sodium bicarbonate. This excretion fell to 17 grams on a diet which was free from alkali, and then rose to 45.2 grams on return to 60 grams of bicarbonate. Such treatment with alkali is sometimes highly beneficial, for, as Magnus-Levy observes, the diabetic does not die in coma because of the neutralized acid which is eliminated in the urine, but rather on account of that which is retained in the body which neutralizes the alkalies of tissue and of body fluids.

Von Noorden[6] reports cases of diabetics who have excreted 5 to 6 grams of aceton and 30 to 40 grams of β-oxybutyric acid in a day, and yet have lived comfortably for years.

Alkali therapy has long been considered important in the treatment of diabetes. Bicarbonate of soda up to 200 grams daily has been given. Weiland[7] cites a case in which green vegetables, 200 grams of meat, and 120 grams of sodium bicarbonate were given daily, under which circumstances the urine contained the following ingredients in grams:

[1] Joslin, E. P.: Arch. Int. Med., 1915, **16**, 693.
[2] Baumgarten, O., and Grund, G.: Deut. Arch. klin. Med., 1911, **104**, 168.
[3] Grafe, E.: *Ibid.*, 1914, **116**, 437; 1923–24, **143**, 1; E. Grafe and von Schröder, E.: *Ibid.*, 1924, **144**, 156.
[4] Deuel, H. J., Jr., Waddell, S. S., and Mandel, J. A.: J. Biol. Chem., 1926, **68**, 801.
[5] Stäubli, C.: Deut. Arch. f. klin. Med., 1908, **93**, 107.
[6] von Noorden, C.: von Leyden's "Handbuch der Ernährungstherapie," 2d ed., Leipzig, 1904, **2**, p. 253.
[7] Weiland, W.: Z. exp. Path. und Therap., 1912–13, **12**, 116.

	Day			
	1	2	3	4
Aceton	14.4	11.8	15.1	13.1
β-oxybutyric acid	90.8	68.4	105.9	90.7
Glucose	138.9	132.0	197.0	89.6
Nitrogen	19.3	15.0	25.0	15.2
Ammonia	1.3	1.1	2.9	1.9

It is evident that, despite the high acidosis, the ammonia is kept at a low level on account of the large amount of alkali administered.

Nothing except dieting affords permanent relief in diabetes.

Mandel and Lusk gave large quantities of yeast to a diabetic man without changing the D:N:: 3.65:1, which shows that the enzymes of yeast are not able to penetrate the intestinal wall so that they may replace the natural ferment of the organism.

Raulston and Woodyatt[1] made an intravenous transfusion of blood from a normal man into a diabetic individual, with aggravation of all the symptoms in the latter.

Minkowski[2] discovered that fructose largely reduced protein metabolism in the case of depancreatized dogs. This led to the widespread use of fructose in diabetes. Mandel and Lusk, however, found that the increase of sugar in the urine of their diabetic man, after giving 100 grams of fructose, was 80 per cent. of the sugar ingested. The fructose had no effect whatever on protein metabolism.

Von Noorden[3] confirms this observation. He believes that fructose is normally produced in metabolism and is normally burned. In very rare cases, called *levulosuria*, fructose alone appears in the urine. One case of complete intolerance for fructose has been reported.[4]

The negative results as regards the value of fructose were especially interesting in the patient of Mandel and Lusk. This diabetic medical student was confident of the efficacy of fructose on account of opinions expressed by the writer in his lectures. On the days of fructose ingestion the patient's spirits revived, his strength, measured on the ergograph, decidedly improved, and his companions remarked upon the benefit received, all of which shows that subjective sensations are not to be used as scientific criteria.

[1] Raulston, B. O., and Woodyatt, R. T.: J. Am. Med. Assn., 1914, **62**, 996.
[2] Minkowski, O.: *Loc. cit.*, p. 131.
[3] von Noorden, C.: *Loc. cit.*, p. 50.
[4] Neubauer, O.: Münchener med. Wchnschr., 1905, **52**, 1525.

CHAPTER XXVI

RENAL GLYCOSURIA. GLUCURONIC ACID. PENTOSES FATTY DEGENERATION. PHOSPHORUS POISONING. HYDRAZIN POISONING

Seek to understand things; their utility will appear later. First of all it is knowledge which matters.—CHARLES RICHET.

IN the anomaly known as renal glycosuria patients utilize carbohydrate just as well as do normal individuals.[1] The blood sugar is usually normal, the renal glycosuria may be quite independent of the ingestion of the food. The glycosuria may be due to a reduced ability of the kidney tubules to absorb glucose. Ladd and Richardson find no reason for believing that it is a preliminary stage of diabetes mellitus.

GLUCURONIC ACID

In this connection it may be mentioned that d-glucuronic acid and pentoses have a bearing on carbohydrate metabolism. A large variety of substances (camphor, chloral, turpentine) form syntheses with glucuronic acid in the organism, and corresponding glucuronates are then eliminated in the urine. Its conjugation with benzoic acid has already been described (see p. 226). At first glance glucuronic acid appears to be the preliminary oxidation product of glucose, as is suggested by the following equation:

$$\underset{\text{Glucose}}{OCH(CHOH)_4CH_2OH} + O_2 = \underset{\text{Glucuronic acid}}{OHC(CHOH)_4COOH} + H_2O$$

However, Mandel and Jackson[2] administered camphor to fasting dogs for several days and noted the excretion of glucuronic acid. On giving large quantities of glucose the protein metabolism fell and with it the glucuronic acid elimination; and on giving the animal chopped meat the quantity of campho-glucuronic acid in the urine was correspondingly increased. It may be safely inferred that glucuronic acid is produced largely in the intermediary metabolism of protein. For

[1] Finley, F. G., and Rabinowitch, I. M.: Quart. J. Med., 1924, **17**, 260; W. S. Ladd and Richardson, H. B.: J. Biol. Chem., 1925, **63**, 681.

[2] Mandel, J. A., and Jackson, H. C.: Proc. Am. Physiol. Soc., Am. J. Physiol., 1902–03, **8**, p. xiii.

the large literature on this subject, and also on the pentoses, the reader is referred to other sources.[1]

Quick[2] finds that a depancreatized dog can still produce glucuronic acid in amount similar to that found in normal dogs. The sugar derived from other sources decreases, indicating a common precursor. The urine analysis in the following experiment bears witness of this fact.

Diet	N	D	Glucuronic Acid	D: N	(D + Glucuronic Acid): N
	Gm.	Gm.	Gm.		
Fasting	4.16	11.2	.....	2.69	
Borneol, 3 gm.	4.07	8.1	1.77	1.98	2.41
Fasting	4.54	11.4	Trace	2.51	

PENTOSES

Pentoses, which are sugars containing 5 atoms of carbon, have been detected in animal and vegetable tissue. Hammarsten found a pentose in the nucleoprotein of the pancreas. Neuberg showed that this pentose and the one obtained from nucleoprotein in the liver is l-xylose.[3] Grund[4] has found pentoses in all organs of the body, particularly in those rich in nuclear material.

Salkowski and Neuberg have shown that l-xylose may be derived through ferment action on d-glucuronic acid. Salkowski was the first to detect a pentose in the urine, and this Neuberg has shown to be i-arabinose. The elimination of pentoses in the urine may accompany diabetes, but in extremely rare cases a simple pentosuria occurs in which pentose is the only sugar appearing in the urine.

Luzzatto[5] reports such a case in which the elimination of arabinose was independent of diet or mental or muscular effort. Luzzatto believes the pentose in this case to have been l-arabinose. Neuberg finds that in the normal rabbit l-arabinose is more readily burned than d-arabinose. Luzzatto's case could be explained by supposing that the body had lost its normal power to burn l-arabinose as normally produced in metabolism.

[1] Neuberg, C.: Ergeb. d. Physiol., 1904, **3,** Pt. 1, 373.
[2] Quick, A. J.: J. Biol. Chem., 1926, **70,** 59.
[3] See also Zerner, E., and Waltuch, R.: Biochem. Z.,1914, **58,** 410; Levene, P. A., and La Forge, F. B., J. Biol. Chem., 1914, **18,** 319.
[4] Grund, G.: Z. physiol. Chem., 1902, **35,** 111.
[5] Luzzatto, R.: Hofmeister's Beitr. chem. Physiol. u. Path., 1905, **6,** 87.

Levene and La Forge[1] suggest the probable presence of d-ribose in the urine of one individual with pentosuria.

Rabinowitch[2] reports of an individual with chronic pentosuria that the utilization of other carbohydrate was unimpaired and that the condition was apparently harmless.

Pentosuria is occasionally discovered in the routine of life insurance examinations. It has long been the common judgment that it does not indicate danger to general health.

Cremer,[3] in a series of excellent experiments, has shown that a vegetable pentose, such as rhamnose, may be burned in a rabbit and spare an isodynamic equivalent of fat. In one rabbit, on a fasting day, the metabolism amounted to 129.1 calories (protein, 22.5, and fat, 106.6), and on the day when rhamnose was given to 128.4 calories (protein, 21.36; fat, 32.9, and rhamnose, 74.11).

Lindemann and May[4] found that 90 grams of rhamnose could be used by a normal man. When, however, rhamnose was given to a diabetic individual whose urine had been sugar free, sugar appeared in the urine. In cases of severe diabetes reported by von Jaksch[5] it was found that rhamnose, arabinose, and xylose tended to increase the protein metabolism, and hence the sugar output, and also brought about diarrhea. The use of pentoses in diabetes has, therefore, not been successful. The pentoses—rhamnose, arabinose, and xylose—are not convertible into glucose in the organism.[6]

As regards xylose, Corley[7] finds that 1 gm. given intravenously to normal or to phlorhizinized rabbits reappears unchanged in the urine. Insulin will not effect its combustion. It has no apparent relation to the combustion of glucose.

FATTY DEGENERATION. PHOSPHORUS POISONING

On autopsy in diabetes large quantities of fat are frequently found in the liver and muscles. The same is observed in chloroform narcosis when sugar appears in the urine, in anemia, and after respiration of rarefied air, when lactic acid is eliminated in the urine (p. 579), and in phosphorus and arsenic poisoning, in acute yellow atrophy, in

[1] Levene, P. A., and La Forge, F. B.: J. Biol. Chem., 1913, **15**, 483.
[2] Rabinowitch, I. M.: J. Clin. Invest., 1925–26, **2**, 457.
[3] Cremer, M.: Z. f. Biol., 1901, **42**, 428.
[4] Lindemann, L., and May, R.: Deut. Arch. klin. Med., 1896, **56**, 283.
[5] von Jaksch, R.: *Ibid.*, 1899, **63**, 612.
[6] Brasch, W.: Z. f. Biol., 1908, **50**, 113.
[7] Corley, R. C.: J. Biol. Chem., 1926, **70**, 521.

pernicious vomiting of pregnancy, in eclampsia and in cyclic vomiting in children, which are similarly accompanied by an elimination of lactic acid. These phenomena are always associated with an increased protein metabolism and an increased ammonia and amino-acid output in the urine.[1] Fat likewise appears in the mammary glands during lactation (see p. 542).

Virchow assumed a fatty degeneration of protein in which the tissue protein was converted into fat, as distinguished from a fatty infiltration in which body fat passed into the cells. Much of the earlier writing of Voit is pervaded with the theory of a considerable origin of fat from protein (p. 271). The idea of a fatty degeneration of protein in the old sense has been largely overturned by the work of Rosenfeld.[2] He found that if a dog be starved and then given sheep's fat, and again starved, the ingested fat was found deposited as sheep's fat in his adipose tissue, while the liver contained about 10 per cent. of fat, and this characteristic dog fat. If now phosphorus or phlorhizin poisoning be induced and the liver be examined, 40 per cent. of fat may be found therein, and this in the form of sheep's fat. Hence, in these cases the fat is simply transported to the liver from the fat deposits of the body. The fat in the blood is largely increased. The fat becomes normal in quantity in the liver twenty-four hours after the cessation of the phlorhizin action. It is retransported to the places of fat deposit.

A supposed production of fat from protein has long been believed to occur in the ripening of cheese. However, Kondo[3] finds that in the process of ripening cheddar cheese 9 per cent. of the original fat content disappears after thirty days and 12 per cent. after forty days.

If a fatty "degeneration" were to be found anywhere, it would certainly be looked for in the dying cells of the liver in phosphorus-poisoning, or in the analogous condition of acute yellow atrophy of the liver. But another explanation avails. Mandel and Lusk[4] have shown that lactic acid disappears from the blood and urine of a phosphorized dog if phlorhizin glycosuria be induced. Lusk believes that the lactic acid which occurs is derived from the sugar formed in protein metabolism. In this case the sugar is removed without conversion into lactic acid. In phlorhizin diabetes, glucose does not

[1] For literature consult Ewing, J.: Arch. Int. Med., 1908–09, **2**, 476.
[2] Rosenfeld, G.: Ergeb. d. Physiol., 1903, **2**, Pt. 1, 50.
[3] Kondo, K.: Biochem. Z., 1913–14, **59**, 113.
[4] Mandel, A. R., and Lusk, G.: Am. J. Physiol., 1906, **16**, 129.

burn; in phosphorus poisoning lactic acid derived from glucose does not burn. In both cases a sugar-hungry cell, or one in which carbohydrate is not oxidized, is found, and under these circumstances fat is attracted to the cell, and in larger quantities than can be useful. Wherever sugar freely burns, this fatty infiltration is impossible (p. 310). A reduced local circulation in a portion of the heart may produce anemia of the part, an imperfect local oxidation of lactic acid normally formed, and a fatty infiltration of the locality. Lusk offers this hypothesis as his explanation of fatty changes in tissue in general.

Laubender[1] has also contrasted the conditions existing in anemia with those found in phosphorus poisoning.

A corroborating fact found by Shibata[2] is that, although the amount of fat in the liver is increased in phosphorus poisoning, the quantity of total fat in the organism is much reduced during the progress of this disease. In cases of fatty infiltration (so-called degeneration) Czyhlarz and Fuchs[3] could find no evidence of an abnormally changed relationship between the quantities of cholesterol and fat present in the diseased tissue.

Medical literature was formerly greatly influenced by the idea of a reduced general oxidation in the body. Except in the case of myxedema which is accompanied by a fall in body temperature, and in some cases of obesity, no such condition occurs. The writer[4] has shown that in phosphorus poisoning, the classical example of supposed reduced oxidation, there was actually no reduction in the total heat production, but rather an increase. From the fourth day to the sixth of simple fasting in one dog the total metabolism for twenty-four hours averaged 45.2 calories per kilogram, and on the ninth day to the eleventh of fasting which preceded death from phosphorus poisoning the heat production was 48.8 calories.

The results of Lusk have been confirmed by Frank and Isaac,[5] who also showed that there was a marked fall in the blood sugar; likewise by Hirz[6] and by Ivančević.[7] The last named noted, in a dog poisoned with phosphorus, death by hypoglycemic convulsions when the blood sugar reached a level of 0.02 per cent.

[1] Laubender, W.: Biochem. Z., 1925, **165**, 427.
[2] Shibata, N.: *Ibid.*, 1911, **37**, 345.
[3] v. Czyhlarz, E., and Fuchs, A.: *Ibid.*, 1914, **62**, 131.
[4] Lusk, G.: Am. J. Physiol., 1907, **19**, 461.
[5] Frank, E., and Isaac, S.: Arch. exper. Path. u. Pharm., 1911, **64**, 274; S. Isaac: Z. physiol. Chem., 1917, **100**, 1.
[6] Hirz, O.: Z. f. Biol., 1913, **60**, 187.
[7] Ivančević, I.: Arch. exper. Path. u. Pharm., 1927, **122**, 24.

Arsenic behaves in the same manner[1] as phosphorus, as does likewise chloranil.[2]

It is therefore evident that the presence of lactic acid is only a symptom in the group of diseases just mentioned (p. 685), and is no more an indication of a reduction in oxidative power as represented by the total heat production than is the elimination of sugar in diabetes. The abundant ammonia in the urine is used to neutralize the acid produced. The reduction in the amount of lactic acid oxidized raises the total protein metabolism. The deficient deamination which results in the elimination of amino-acids in the urine is due to the injury done to the functioning of the liver (see p. 579).

It has been stated that the action of phosphorus is to induce autolysis (self-digestion) of the body's protoplasm (Jacoby,[3] Waldvogel[4]), since leucin, tyrosin, glycin,[5] phenyl-alanin and arginin,[6] and other amino-acids may be eliminated in considerable quantity in the urine. Wakeman[7] finds a change in the relative amounts of histidin, arginin, and lysin contained in the liver substance after phosphorus poisoning, arginin in particular being reduced below the quantity found in the liver of the normal dog. Oswald[8] thinks that phosphorus destroys or weakens the anti-autolytic agents of the body. That autolytic enzymes do not gain free control over the cells through the direct influence of phosphorus is proved by the work of Ray, McDermott, and Lusk.[9] These authors found that phosphorus injections raised the protein metabolism of fasting dogs to 250, 260, 283, 248, 183, and 164 per cent. of that of the dog when normal. They contrasted this increased protein metabolism with that obtained in phlorhizin glycosuria, which is represented by increases to 540, 450, 340, and 340 per cent. When, however, they gave phlorhizin and obtained the increased metabolism, and then injected phosphorus, *this was not followed by any marked increase in protein metabolism.* Under these circumstances phlorhizin glycosuria is the predominating factor, removing the glucose produced from protein before it could be converted into lactic acid under the influence of phosphorus.

[1] Hildebrandt, F., and Nishiura, S.: Arch. exp. Path. u. Pharm., 1924, **101,** 161.
[2] Staub, H.: Biochem. Z., 1926, **179,** 125.
[3] Jacoby, M.: Z. physiol. Chem., 1900, **30,** 174.
[4] Waldvogel: Deut. Arch. klin. Med., 1904–05, **82,** 437.
[5] Abderhalden, E., and Bergell, P.: Z. physiol. Chem., 1903, **39,** 464.
[6] Wolgemuth, J.: *Ibid.*, 1905, **44,** 74.
[7] Wakeman, A. J.: *Ibid.*, 1905, **44,** 335.
[8] Oswald, A.: Biochem. Centralbl., 1904–05, **3,** 365.
[9] Ray, W. E., McDermott, T. S., and Lusk, G.: Am. J. Physiol., 1899–1900, **3,** 139.

As regards phosphorus poisoning Araki[1] believes that lactic acid accumulation is due to lack of oxygenation of the tissues caused by a slow heart-beat, but not due to anemia. He does not believe the oxygen deprivation to be very pronounced. The accumulation of lactic acid and its non-combustion may necessitate an increase of protein metabolism.

Claude Bernard showed that glucose, whether derived from protein or starch, was convertible into glycogen, and this again was changeable into glucose. Present knowledge adds lactic acid to both ends of this chain in showing the following possible progression—lactic acid, glucose, glycogen, glucose, lactic acid (see p. 332).

Quite pertinent to this theoretic discussion is the observation of von Jaksch[2] on a patient who recovered from phosphorus poisoning, and in whom a desire for carbohydrates marked the beginning of convalescence.

It should also be noted that more carbohydrates must be ingested in cases of hepatic disease to maintain nitrogen equilibrium than are required in health.[3]

HYDRAZIN POISONING

A curious anomaly of carbohydrate metabolism has been discovered by Underhill[4] following the administration of hydrazin, which he defines as a poison with an almost specific effect upon the cytoplasm of the parenchymatous cells of the liver. It attacks first the cells in the center of the lobules, while phosphorus shows its first effects upon the cells of the periphery. If 50 milligrams of hydrazin per kilogram of animal be given to dogs, the quantity of glucose in the blood and of glycogen in the liver is greatly reduced and the administration of glucose may cause the death of the animal within twelve hours. Otherwise the dog recovers in five days. Underhill and Murlin[5] found that the administration of hydrazin to fasting dogs increased the respiratory quotient. An increased oxidation of carbohydrate, therefore, probably explains the diminished blood-sugar content and the disappearance of glycogen from both liver and muscles. Hydrazin was without influence upon the level of the basal metabolism.

[1] Araki, T.: Z. physiol. Chem., 1893, **17**, 337.
[2] von Jaksch, R.: *Ibid.*, 1903–04, **40**, 123.
[3] Tallqvist, T. W.: Arch. f. Hyg., 1908, **65**, 39.
[4] Underhill, F. P.: J. Biol. Chem., 1911–12, **10**, 159.
[5] Underhill, F. P., and Murlin, J. R.: *Ibid.*, 1915, **22**, 499.

CHAPTER XXVII

METABOLISM IN NEPHRITIS, IN CARDIAC DISEASE, AND IN OTHER CASES INVOLVING ACIDOSIS

The physiology of the body is not completed. If it were medicine would be a science and not an art. But the certainty with which disease is treated depends upon knowledge of healthy function. Where this is complete or nearly so there is light, where it is absent, blind empiricism.—William T. Lusk (b. 1838), unpublished paper.

In 1821 Prevost and Dumas[1] observed that if the kidneys of a dog be extirpated, urea accumulates in the blood. This observation led to the discovery by Bright in 1836 that the amount of urea in the blood of nephritic patients was abnormally high.

Using more accurate methods, Folin[2] finds that when a low protein dietary is taken the normal figures for total non-protein nitrogen in the blood of a man are 22 to 28 milligrams per 100 c.c. of blood, of which 11 to 14 milligrams are in the form of urea. The maximum amount of non-protein nitrogen in a normal person is not usually above 40 milligrams per 100 c.c.[3] Sometimes after protein ingestion in nephritis the non-protein nitrogen does not increase in the blood; in other cases there is a considerable rise. The increased level of urea in the blood is a compensatory reaction to a diminished power of excretion by the kidney.[4]

Emphasis has been laid upon a positive nitrogen balance as indicating a retention of urea by the nephritic patient, but such a retention is susceptible of two interpretations. Thus, Mosenthal and Richards[5] have given patients with moderately severe chronic interstitial nephritis diets containing between 16 and 47 grams of nitrogen and have observed nitrogen retention. Had this retention been in the form of non-protein nitrogen, the blood would have contained between 78 and 148 milligrams of such nitrogen, but the actual values never rose above 38 milligrams. Davis and Foster,[6] however, find that

[1] Prevost and Dumas, J.-B.: Ann. de chimie et de phys., 1821, **23,** 90.
[2] Folin, O., Denis, W., and Seymour, M.: Arch. Int. Med., 1914, **13,** 224.
[3] For the complete chemical and physical analysis of blood in 30 normal cases consult the important work of Gettler, A. O., and Baker, W.: J. Biol Chem., 1916, **25,** 211.
[4] McLean, F. C.: J. Exp. Med., 1915, **22,** 366.
[5] Mosenthal, H. O. and Richards, A. E.: Arch. Int. Med., 1916, **17,** 329.
[6] Davis, H., and Foster, N. B.: Proc. Soc. Exp. Biol. and Med., 1915–16, **13,** 33.

nitrogen retention under these circumstances may take place in the liver and muscle in the form of non-protein nitrogen. The very ill patients were benefited by large water ingestion.

Henderson and Palmer[1] describe cases of nephritis in which the volume of the urine is large, the titratable acidity high, but in which the total acid elimination is decreased because of a greatly reduced elimination of ammonia. They conclude that this points to a condition of acidosis of renal origin. As a matter of fact, Peabody[2] has discovered that the acidosis of nephritis is due to a retention of non-volatile acids which would ordinarily be removed by the kidney. The acid retained is acid phosphate.[3] Chace and Myers[4] state that all fatal cases of chronic nephritis with marked nitrogen retention show a severe acidosis, sufficient in many instances to be the actual cause of death.

Aub, and DuBois,[5] have made investigations concerning the metabolism of 10 patients suffering from severe nephritis which show that most of the individuals had normal basal metabolisms. In the presence of greatly decreased alkalinity and of a high content of non-protein nitrogen in the blood the total heat production showed no variation from the normal. In patients with severe edema the basal metabolism fell to −27 and −40 per cent. of the normal. Most of the patients who had marked dyspnea showed an increase in the metabolism.

Neubauer[6] was the first to observe the presence of hyperglycemia in nephritis. Linder, Hiller, and Van Slyke[7] find that in severe renal insufficiency in glomerulonephritis there is a prolonged and exaggerated rise in the blood sugar curve after giving glucose by mouth, and glycosuria sets in. The respiratory quotient rises as rapidly as in normal people, indicating a normal oxidation of glucose. Some other factor causes the rise in the blood sugar, perhaps retarded glycogen formation.

Strouse and Kelman[8] state that in frank progressive nephritis with hypertension a diminution of protein intake sufficient to reduce the non-protein nitrogen of the blood did not reduce the blood pres-

[1] Henderson, L. J., and Palmer, W. W.: J. Biol. Chem., 1915, **21**, 37.
[2] Peabody, F. W.: Arch. Int. Med., 1914, **14**, 236; *Ibid.*, 1915, **16**, 955.
[3] Marriott, W. McK., and Howland, J.: *Ibid.*, 1916, **18**, 708.
[4] Chace, A. F., and Myers, V. C.: J. Am. Med. Assn., 1920, **74**, 641.
[5] Aub, J. C., and DuBois, E. F.: Arch. Int. Med., 1917, **19**, 865.
[6] Neubauer, E.: Biochem. Z., 1910, **25**, 284.
[7] Linder, G. C., Hiller, A., and Van Slyke, D. D.: J. Clin. Invest., 1924–25, **1**, 247.
[8] Strouse, S., and Kelman, S. R.: Arch. Int. Med., 1923, **31**, 151.

sure. Also that protein ingestion up to 150 gm. daily by patients with hypertension and no impairment of renal function did not change the blood pressure. Strong soup stock and coffee also were without effect.

It has been reported by Newburgh[1] that when rabbits eat the whites of several eggs daily they develop nephritis. Casein produces the same effect, though urea ingestion is without influence. Jackson and Riggs,[2] however, have given diets rich in protein to many rats for a third of their lifetimes and have found no evidence of the development of chronic nephritis.

Tachau[3] finds that in nephritis the loss of organic nitrogen by way of sweat induced by an electric light bath is not material, but that the loss of sodium chlorid may reach 2 grams per hour and may reduce an edema.

CARDIAC DISEASES

In patients who manifest marked evidence of circulatory disturbances Foster[4] shows that there is an increase in the quantity of non-protein nitrogen of the blood, even in the absence of nephritis.

Peabody, Meyer, and DuBois[5] studied 16 patients with cardiac and cardiorenal disease by the methods of direct and indirect calorimetry. The two methods agreed within 1.9 per cent. There was no abnormal deviation of the respiratory quotients as had been announced by several previous investigators. Patients with compensated cardiac lesions or with mild nephritis showed a normal metabolism. Of 12 patients with dyspnea, 9 showed a distinct rise in metabolism, and in 5 of these the increase was between 25 and 50 per cent. above the normal. Two of these 5 patients manifested marked acidosis, as was indicated by a low carbon dioxid tension in the alveolar air. In 2 other patients, whose metabolisms were equally high, there was no significant depression of the alveolar carbon dioxid.

If the dyspnea were accompanied by the production of lactic acid in any of the organs, this might have been the stimulus to the higher metabolism observed. The decompensated heart produces slow or

[1] Newburgh, L. H.: Arch. Int. Med., 1919, **24,** 359.
[2] Jackson, H., Jr., and Riggs, M. D.: J. Biol. Chem., 1926, **67,** 101.
[3] Tachau, P.: Deut. Arch. klin. Med., 1912, **107,** 305.
[4] Foster, N. B.: Arch. Int. Med., 1915, **15,** 356.
[5] Peabody, F. W., Meyer, A. L., and DuBois, E. F.: *Ibid.*, 1916, **17,** 980.

insufficient circulation with imperfect oxidation in the tissues, which conditions readily lend themselves to lactic acid formation.

Continuing this work, Peabody, Wentworth, and Barker[1] analyzed the differences in the metabolism of 24 cardiac patients, in whom 10 had a vital capacity which was above 60 per cent. of the normal value and 14 a vital capacity less than 60 per cent. of the normal. The average results obtained from the two groups were as follows:

	Vital Capacity over 60 Per Cent. Normal	Vital Capacity under 60 Per Cent. Normal
Vital capacity, c. c.	3467	1948
R. Q.	0.83	0.79
Basal metabolism, per cent.	+2.5	+12.8
Respiration rate per minute	13	22
Minute volume	6.0	8.6
Average volume, one respiration	471	408

The second group all had nephritis. In these patients the air was not thoroughly mixed with alveolar air because of bronchitis, edema, etc. The authors believe that the various abnormal findings in patients with severe heart disease may be explained on the basis of a decrease in the vital capacity of the lungs associated with a diminished respiratory surface.

Shapiro[2] confirms these conclusions, stating that the basal metabolism is normal in a patient with cardiac overactivity, such as occurs in a heart compensating for an organic heart defect or maintaining an elevated vascular tension. The elevation in metabolism, when it does occur, is due to dyspnea. (Compare with anemia on p. 581.)

Howland and Marriott[3] describe a type of acidosis which occurs in infants during the course of attacks of severe diarrhea not of ileocolitic type. The usual type of abdominal breathing of the young child is succeeded by one which is both costal and abdominal. There is a greater amplitude in the respirations and they are made with a distinct effort. There is no cyanosis. The condition was first described by Czerny[4] who called attention to the symptoms as resembling those observed in rabbits dying after the administration of mineral acids. Howland and Marriott find that a condition of

[1] Peabody, F. W., Wentworth, J. A., and Barker, B. L.: Arch. Int. Med., 1917, **20**, 468.
[2] Shapiro, S.: *Ibid.*, 1926, **38**, 385.
[3] Howland, J., and Marriott, W. M.: Am. J. Dis. Child., 1916, **11**, 309.
[4] Czerny, A.: Jahrb. f. Kinderh., 1897, **45**, 271.

acidosis is actually present in these children and they were the first to use alkaline treatment in order to rescue them. The acidosis is not due to aceton bodies, from which the blood is free.

The following presents the results of treatment in one of their cases:

	Date	Alveolar CO_2 Tension	Hyperpnea	Alkali
		Mm.		
Case I.	22	21	+++	Given.
	23	42	o	Given.
	24	54	o	Stopped.
	24	55	o	
	25	41	o	

In normal infants the carbon dioxid tension is between 36 and 45 mm. and the pH of the blood is 7.4. In the children with acidosis the pH of the blood was 7.2. There was also a reduction of the reserve alkali of the blood. There was frequent anuria and the conclusion is drawn that the cause of the acidosis is probably a retention of acid phosphate in the organism.

CHAPTER XXVIII

METABOLISM IN FEVER

Every fundamental *Arbeit* must be one based upon the fundamental laws of energy.—Wilhelm Ostwald.

By fever is generally understood a complex of phenomena the dominant characteristic of which is a rise of body temperature. If the term "fever" be confined simply to the latter aspect, one might classify fevers as follows:

(1) *Physiologic fever*, induced, for example, by immersion in a hot bath at a temperature of 40°, which prevents the normal loss of body heat through radiation and conduction. (2) *Neurogenic fever*, as brought about by the direct stimulation of nerve-cells in the *corpora striata* of the mid-brain. (3) *Non-infective surgical fever*, commonly called *aseptic fever*, due to the resolution of blood-cells or crushed tissue in the organism. (4) *Infective fever*, produced after the infection of the organism by certain bacteria or their products and by some protozoa. Or one may consider fever as being due to infection by bacteria or protozoa, and include all other increases of temperature under the term of *hyperthermia*.

In a previous chapter the mechanism of normal heat regulation has been explained. It was there noted that on a warm, moist day the temperature of a fat individual, when he was working hard, rose considerably above the normal. This effect, if carried to an extreme, results in *sunstroke*, in which overheating of the body causes a rapid pulse, accompanied by dizziness, delirium, or unconsciousness. But in the great majority of cases the body temperature remains delicately balanced, notwithstanding changes in outside environment, or internal heat production. In the fat person at hard work the condition of increased metabolism is combined with that of difficult discharge of heat. A person placed in a bath at 40° would be subject to conditions where there could be no heat loss, but rather a gain in heat, even though his metabolism were low. In a normal person, therefore, a rise in temperature may be due to increased heat production, with difficulty in discharging it, or a check of heat loss may be

the only factor of the higher temperature. In the discussion of fever one must consider two possible causes: (1) an increase in heat production, and (2) a decrease in the facilities for the discharge of heat produced.

PHYSIOLOGICAL FEVER

It has already been set forth that the metabolism in a cold-blooded animal increases with the temperature of his environment. Warmed tissue metabolizes more material than cooled tissue. It is therefore to be expected that the metabolism in an organism which has been warmed to fever heat will be greater than the normal. This was beautifully shown in the experiments of Pflüger,[1] who subjected both curarized and normal rabbits to external warmth which raised their temperatures. In the animals whose voluntary muscles were paralyzed by curare as the rectal temperature rose from 39° to 41° the oxygen absorption increased 10 per cent. for each degree of temperature increase. In the normal animals the increased metabolism between temperatures of 38.6° and 40.6° was shown by increases of 5.7 per cent. for oxygen and 6.8 per cent. for carbon dioxid for a rise of 1° of temperature. Compare this with the chart of Krogh given on p. 119.

It has been noted in another chapter (p. 157) that Rubner found in man that a bath at a temperature of 35° had no effect on metabolism, while one at 44° increased the volume of respiration 18.8 per cent., the oxygen absorption 17.3 per cent., and the carbon dioxid elimination 32.1 per cent. Linser and Schmid[2] confirm these results in experiments on two men suffering from *ichthyosis hystrix*, which involved almost complete loss of function of the sweat-glands. The body temperature of these men could be varied by altering the temperature of their living-room between 30° and 38°. The humidity of the room was from 40 to 50 per cent. The maximum increase in the metabolism of these individuals is represented by a rise in carbon dioxid excretion from 3.8 c.c. per minute and kilogram at the body temperature of 36.2° to 5.3 c.c. per minute and kilogram at 39°. The number of respirations, which were from 12 to 15 per minute at 36°, increased to 20 and 22 at 39°. The total increase in the carbon dioxid output, due to a rise of 3° through simple warming of cells,

[1] Pflüger, E.: Pflüger's Arch. gesam. Physiol., 1878, **18**, 303, 356.
[2] Linser, P., and Schmid, J.: Deut. Arch. klin. Med., 1904, **79**, 514.

amounted to 40 per cent. The inadequate evaporation of water caused a rise of body temperature when the surrounding air was hot.

Loewy and Wechselmann[1] showed that there was an excretion of water through the skin of persons who were devoid of sweat glands, (see p. 144). Richardson[2] has studied a boy 14 years of age who was without sweat glands. The boy could not play in the summer time because he became too hot and had to stop. He was comfortable when quiet. He wet his shirt to promote cooling. The following factors were found when the boy was resting or executing mechanical work.

	Congenital Absence of Sweat Glands		Normal Man	
	Rest	35 Minutes' Work	Rest	45 Minutes' Work
	Cals. per Sq. M.	Cals. per Sq. M.	Cals. per q. M.	Cals. per Sq. M.
Radiation and conduction	32.3	52.7	27.7	46.3
Vaporization of water	12.3	17.3	8.8	19.5
Heat eliminated	44.6	70.0	36.5	65.8
Rectal temperature	(37.97°)	(38.65°)	(36.61°)	(37.02°)
Body change correction	−5.0	+29.9	−2.8	+22.8
Total heat: direct calorimetry	39.7	100.0	33.7	88.6

The water vaporized by the normal man during mechanical exercise corresponded to 26 per cent. of the total heat directly calculated, and his body temperature rose 0.41°. In the boy with congenital absence of sweat glands the loss of heat by water vaporization was only 17 per cent. of the total, and his temperature rose 0.67°.

Richardson concludes that even without sweat glands there is an increased evaporation of water at the surface during mechanical exercise, because there is then more blood brought to the surface, and that the sweat glands merely furnish an emergency cooling apparatus for use under exceptional circumstances.

The next question is of the nature of the materials which are oxidized. It has long been known that urea excretion is abnormally high in fever,[3] and this led to the inquiry whether the rise was merely

[1] Loewy, A., and Wechselmann, W.: Arch. Path. Anat., 1911, **206**, 79.
[2] Richardson, H. B.: J. Biol. Chem., 1926, **67**, 397.
[3] Traube, L., and Jochmann, P.: Deut. Klin., Berlin, 1855, **7**, 511.

the result of increased body temperature or was due to toxic influences.

The Protein Metabolism in Hyperthermia.—F. Voit[1] found that on artificially raising the temperature of a fasting dog to 40° or 41° for a period of twelve hours there was an increase in nitrogen elimination of 37 per cent. above the normal. Warming for a period of only three hours had slight effect. If, however, the animal were fed with meat and fat, warming increased the protein metabolism only 4 per cent. If the animal received 30 to 40 grams of cane-sugar no increased metabolism of protein followed the rise in temperature to 41°. It is apparent that the ingestion of protein and carbohydrates may control this rise in protein destruction due to a febrile temperature. F. Voit explains the increase in protein metabolism in hyperthermia as due to the quick combustion of glycogen and the consequent impoverishment of the tissues as regards carbohydrate material. Protein or carbohydrate ingesta furnish the necessary carbohydrate and prevent the hyperthermal rise in protein metabolism.

Careful experiments by Graham and Poulton,[2] conducted in Friedrich Müller's clinic in Munich, have shown that in man a body temperature of 40.2°, brought about by the influence of a steam bath, does not of itself cause an increase in the metabolism of body protein. Three different diets were taken. In experiments I and II the caloric value of the diet was high, with excess of carbohydrate and only a minimal quantity of protein. Diets III and IV were composed chiefly of protein and fat; one with ample calories and high in protein, the other with insufficient calories and only a moderate amount of protein. The results of the experiments may be thus epitomized:

Subject	P.	G.	P.	G.
Experiment	I	II	III	IV
Character of diet	CH + fat.	CH + fat.	Prot. + fat.	Prot. + fat.
Calories in diet	4950	4690	3700	1970
Calories per kg. per day	68	75	50	32
N in diet, grams	1.23	0.91	34.4	12.3
No. of days of diet before experiment	6	6	19	8
± Body N, day before bath	−3.37	−3.00	+1.91	−3.41
± Body N, day of hot bath	−2.88	−2.78	+1.42	−2.45
± Body N, day after bath	−2.85	−2.47	+1.66	−3.22
Maximal body temperature, day of bath	39.3°	40.2°	40.1°	39.7°

[1] Voit, F.: Sitzungsber. Gesel. Morph. u. Physiol., 1895, 11, 120.
[2] Graham, G., and Poulton, E. P.: Quart. J. Med., 1912, 6, 82.

In these experiments the abnormally high body temperature was maintained for several hours, and yet there was never any increase in the breakdown of body protein due to the hyperthermia.

It has already been recited (see p. 407) how Kocher, working in the same clinic, found that a walk of 60 kilometers with a consequent doubling of the heat production was without effect upon the protein metabolism even when the output of urinary nitrogen was at a minimal level.

It is evident from these experiments that neither high body temperature nor largely increased heat production has any effect upon the minimal wear and tear quota of protein metabolism. The destruction of protein by toxic processes in fever is, therefore, independent of the two factors enumerated, as will be seen later.

NEUROGENIC FEVER

If certain portions of the brain be punctured, and particularly the region of the *corpora striata*, a high fever sets in. Here again there is an increased output of carbon dioxid and a rise in protein metabolism. This phenomenon has been notably investigated by Hirsch, Müller, and Rolly,[1] and by Rolly[2] alone. They find that after the "heat puncture" of the corpora striata the liver, blood, and skin become warmer than the muscles, although normally the muscles are warmer than the skin. They find that the heat puncture is effective even in curarized animals, in which the muscles are free from nerve stimuli. Rolly finds, however, that the heat puncture is ineffective if the liver of the rabbit has been previously freed from glycogen by strychnin convulsions. Under these circumstances there is no rise in temperature nor concomitant rise in protein metabolism. The inference is that the fever in question is due to nerve impulses which increase the metabolism of carbohydrate in the liver. In infectious fever there is little glycogen in the organism, but that the fever in this case is due to other causes than the rapid combustion of carbohydrates was shown by Rolly, who infected a rabbit, which had been freed from glycogen as above described, with a culture of pneumococci and obtained as great a rise in temperature and protein metabolism as would have occurred had the tissues of the rabbit been

[1] Hirsch, K., Müller, O., and Rolly, F.: Deut. Arch. klin. Med., 1903, **75**, 264.
[2] Rolly, F.: *Ibid.*, 1903, **78**, 250.

rich in carbohydrates. The rise in temperature after puncture of the corpora striata may be termed *neurogenic fever*, and it is like the glycosuria following Claude Bernard's puncture, in that its mechanism is no more invoked in true infectious fever than are the nerve centers in diabetes mellitus (p. 616).

Freund[1] finds that simple heat puncture in the rabbit is still effective after cutting the cord at the level of the second dorsal nerve. It is interesting that this phenomenon of heat puncture, with its increased carbohydrate combustion and an elevation of body temperature between 0.7° and 1.76° in rabbits and in dogs, is without influence upon the hydrogen ion concentration of the blood.[2]

EXPERIMENTAL INFECTIVE FEVER

Wood[3] in 1880 found an average increase of 23 per cent. (calculated by Welch) in the heat production of fasting dogs after inducing fever; and he also found that mere ingestion of food by a normal dog would cause a greater heat production than fever itself.

If the extent of metabolism in infectious fevers be investigated the following state of affairs is discovered. The course taken by the metabolism in toxic fevers is, as a rule, (1) a slight rise in protein metabolism, even before the fever sets in; (2) increased metabolism with heat retention and increased protein destruction; (3) heat production and heat elimination become equal, with the body at a higher temperature level. These factors were illustrated in the experiments of May[4] on fasting rabbits injected with a culture of erysipelas of the pig and in the following experiments of Staehelin.

Staehelin[5] infected a dog by inoculating him with 1.5 c.c. of dog's blood containing surra trypanosomes, which are active flagellate parasites. Fever set in on the sixth day after the inoculation and the dog died on the twenty-fifth day. The metabolism due to the infection rose to 88.9 calories per kilogram on the tenth day after inoculation as against a normal of 59.8, an increase of 48 per cent. On this febrile day 26 per cent. of the total energy was yielded by protein; the body lost 2.8 grams of nitrogen, which indicated a high toxic waste.

[1] Freund, H.: Arch. exp. Path. u. Pharm., 1913, **72,** 304.
[2] Quagliariello, G.: Biochem. Z., 1912, **44,** 162.
[3] Wood, H. C.: "Fever," Smithsonian Contributions to Knowledge, No. 23, Washington, 1880.
[4] May, R.: Z. f. Biol., 1894, **30,** 1.
[5] Staehelin, R.: Arch. f. Hyg., 1904, **50,** 77.

However, all the increase in the heat production did not come from increased protein metabolism, but the fat destruction was also increased, and Staehelin speaks of a toxic waste of fat. He also remarks that the dog remained perfectly quiet during the period of the experiment, but he does not say whether thermal influences which could result in chill were completely excluded. However, he came to the conclusion that in this fever caused by trypanosomes the metabolism was higher than could be explained by the overwarming of the body.

During the last days of life the body temperature fell and with it the amount of the metabolism. The following table gives a partial record of the daily metabolism in this dog:

METABOLISM IN FEVER INDUCED BY SURRA TRYPANOSOMES

Period	Day after Inoculation	No. of Days in Period	Grams N in Food	Grams N to Body	Calories in Food	Calories of Metabolism	Calories per Kg.	Calories per Sq. M. Surface	Body Temp.	
									Max.	Min.
I. Normal (average)	.....	..	5.67	+0.15	585	510.0	59.8	1027		
II. Inoculation and prodromal	6	6	5.67	−0.18	585	469.3	58.3	982	39.4	38.3
III. 1st of fever	7	4	5.67	−0.40	585	521.4	63.9	1081	39.5	38.3
	8	..	5.67	−0.46	585	556.9	68.2	1154	39.6	37.7
	9	..	5.67	−1.06	585	675.2	81.6	1388	40.1	39.6
	10	..	5.67	−2.80	585	729.3	88.9	1507	39.2	37.9
IV. 2d of fever (average)	11–17	7	4.37	−2.50	451	665.2	83.7	1404		
V. 3d of fever (average)	18–20	3	3.34	−2.52	348	665.0	74.0	1218	40.4	38.5
VI. Final period (average)	21–24	4	....	−4.63	...	521.0	62.0	907	38.8	35.5

Nebelthau[1] has shown a fall in temperature and heat production in a rabbit whose cord was divided between the sixth and seventh cervical vertebræ, and has also demonstrated that under these circumstances infection with erysipelas of the pig had no influence on temperature or heat production. The inference is that the febrile toxins act through the higher vasomotor centers, whose regulatory control is lost in the experiment cited above.

A kindred interpretation may be placed on the experiments of Mendelson,[2] who was unable to produce fever through pus injections when the dog was under the influence of chloral or morphin, although

[1] Nebelthau, E.: Z. f. Biol. 1895, **31**, 353.
[2] Mendelson, W.: Virchow's Arch. path. Anat., 1885, **100**, 274.

such treatment in a normal animal caused a rise in temperature of from 36.3° to 39.9° in forty-five minutes. Mendelson also finds a constant constriction of the renal blood-vessels in fever.

Further experimentation convinced Sawadowski[1] that fever cannot be produced after the mid-brain has been severed from the medulla, whereas if the mid-brain be left intact, but the cerebrum be sectioned from it, fever may be induced in the ordinary course. Citron and Leschke[2] have found that destruction of the median portion of the 'tween brain on the boundary between the optic thalamus and the corpus quadrigeminum anterius, the "'tween brain puncture," converts a rabbit into the equivalent of a cold-blooded animal. Under these circumstances it is impossible to produce infective or non-infective fevers of any kind. The toxic substance must therefore act on nerve-cells in the mid-brain, which, in turn, stimulate the medullary centers.

On autopsy of patients who have died of fevers, parenchymatous and fatty degenerations of the organs have been found. These changes have been ascribed to overheating of the cells.

Litten[3] warmed guinea-pigs artificially and noted fatty but no parenchymatous degeneration of the tissues. The space in which the animals were kept was, however, insufficiently ventilated, and the fatty change might have been caused by dyspnea, as results in normal animals (p. 579).

Naunyn[4] observed that rabbits might be artificially warmed for thirteen days, so that an average body temperature of 41.5° was maintained without any parenchymatous or fatty degeneration taking place. The animals were supplied with ample food, water, and a sufficient supply of air. Naunyn found that the red blood-cells of rabbits and dogs remained intact even at a body temperature of 42°. Welch[5] noticed fatty but no parenchymatous change in the tissues of rabbits after exposure to high temperature for at least a week. One rabbit which had been subjected to high temperature for four days was inoculated with the bacilli of the swine plague and died in thirty-six hours, showing extreme fatty changes in the heart and other organs.

[1] Sawadowski, J.: Centralbl. med. Wissensch., 1888, **26**, 161.
[2] Citron, J., and Leschke, E.: Z. exp. Path. u. Therap., 1913, **14**, 379.
[3] Litten, M.: Virchow's Arch. path. Anat., 1877, **70**, 10.
[4] Naunyn, B.: Arch. exp. Path. u. Pharm., 1884, **18**, 49.
[5] Welch, W. H.: Med. News, 1888, **52**, 403.

Ziegler[1] discovered degenerative changes, both parenchymatous and fatty, on artificially warming rabbits. The experiment was continued in one case for twenty-nine days. He found, however, a great reduction (30 per cent. and more) in the quantity of hemoglobin in his rabbits. It may well be a question whether the fatty change noticed in the liver and muscles was not due to anemia instead of to the hyperthermia. Since fatty infiltration is known to be caused by dyspnea, which frequently terminates life in fever, one might investigate this subject to see whether parenchymatous change in fever is not sôlely due to the toxins, and fatty change to the anaërobic cleavage of materials in the cells, which always induces fatty infiltration (p. 685).

Rosenthal[2] states that if diphtheria toxin be administered to rabbits the liver is rendered incapable of retaining glycogen. There is hypoglycemia except following glucose administration, when a hyperglycemia greater than that possible in normal animals occurs.

FEVER IN MAN

Traube,[3] who was the first modern scientific clinician, attributed the cause of fever to a cramp-like constriction of the peripheral arterioles, which prevented the proper distribution of the blood at the surface and therefore hindered the normal cooling of the body. Since Traube's writings on the subject were published the cause of fever has been attributed not to greater heat production, but to a disturbance in the mechanism of the regulation of heat loss. On recalling the fact that the metabolism of a man may be raised from 100 calories to 146 calories after giving meat (see p. 284) without a material change of body temperature, it becomes evident that the increased heat production in fever cannot alone be the cause of the body temperature. In fact, as has already been set forth, the rise in the body temperature from failure of the physical regulation may of itself explain the increase in heat production.

Senator[4] early recognized that the increase in body temperature took place in consequence of a disturbed relationship between an abnormally high heat production and a heat elimination not corre-

[1] Ziegler, E.: Verhandl. XIII, Kong. inn. Med., 1895, Sect. 3, p. 345.
[2] Rosenthal, F.: Arch. exp. Path. u. Pharm., 1914, **75,** 99.
[3] Traube, L.: Allgemeine med. Central-Zeitung, 1863, **32,** 410, 426, 810.
[4] Senator, H.: *Ibid.*, 1868, **37,** 926; and "Untersuchungen über den fieberhaften Prozess," Berlin, 1873.

spondingly high. Senator assumed an increase in the production of heat, which Traube did not. Leyden[1] found a considerable increase of metabolism in fever.

The effect of a cold bath upon a vigorous man is to constrict the peripheral blood-vessels and to increase the heat production. The body temperature, instead of falling, may rise for eight or ten minutes and then sink.[2] If the individual pass from the bath during the earlier minutes the hot blood comes to the surface to be cooled, and the body glows with a red color, the so-called "reaction." This experiment shows that there are factors invoked during the first few minutes which prevent the discharge of the heat produced. One factor must be a general constriction of the peripheral arteries, causing the blood to remain in the heat-producing inner organs of the body. In this experiment, therefore, cooling of the organism is prevented by the mechanism of physical regulation above described, and the mechanism of chemical regulation which reflexly increases heat production.

To combat a rise in temperature, however, the only means available is the physical regulation—*i.e.*, the change in the distribution of the blood and the production of sweat. If these avenues of heat loss be diminished or shut off, heat accumulates within the body and the temperature rises. Why an increase in heat production of 55 per cent. after meat ingestion may not cause a rise in temperature in a normal man has already been explained; whereas, a high fever may be accompanied by much less of an increase in metabolism. The cause of the fever must, therefore, be a diminution in the ability to discharge the heat produced.

The phenomena of fever have been investigated with especial care with the respiration calorimeter of the Russell Sage Institute of Pathology at Bellevue Hospital. The mechanism of fever could be studied with this apparatus with greater precision than ever before.

MALARIAL CHILL

Liebermeister[3] was the first to investigate the metabolism in malarial chill. He found that the body temperature of his patient rose from 36.9° to 39.5° as the result of the paroxysm, while the

[1] Leyden, E.: Deut. Arch. klin. Med., 1870, **7**, 536.
[2] Lefèvre, J.: Compt. rend. soc. biol., 1894, **46**, 604.
[3] Liebermeister, C.: Deut. Arch. klin. Med., 1871, **8**, 153.

carbon dioxid expired rose from 14.85 gm. per half hour to 34.2 gm., an increase of 130 per cent.

A patient of Barr and DuBois[1] was investigated with the Sage respiration calorimeter. The basal metabolism was determined an hour or more before the chill and was found to be 14 per cent. above the normal, although the body temperature itself was normal. Then followed a short period of 15 to 20 minutes immediately before the chill, during which the temperature rose and the patient began to feel uncomfortable. This rise of body temperature was a warning to the investigators to prepare the calorimeter so that the onset of the chill might approximately coincide with the beginning of an experimental period. A violent chill ensued which lasted for 40 minutes and which increased the metabolism 216 per cent. This may be compared with an increase of 180 per cent. in a normal man during violent shivering in a cold room following exposure to a bath containing blocks of ice.[2] The rectal temperature of the malarial patient rose 2° as the result of the chill. The total heat eliminated during this period rose only very slightly above the amount eliminated before the chill, and the water elimination remained almost constant. Before the chill 28 per cent. of the calories eliminated were lost by the vaporization of water, and during the paroxysm 31 per cent. The excess of calories produced by the chill were stored in the body and raised the body temperature because the normal avenues of escape of such heat were closed by the constriction of the arterioles and the lack of response of the water vaporizing system. In other words, there was a disturbance of the mechanism for the physical regulation of the temperature of the body. The respiratory quotient was 0.86, a not unusual basal value.

During the 60 minutes following the chill the heat production remained at 80 per cent. above the normal, the heat elimination increased but did not reach the heat produced, and the rectal temperature rose 1.3° further. During the second hour after the chill the heat production was maintained at 71 per cent. above the basal level. This is the period of high continuous temperature which corresponds to the clinical stage of heat. The rectal temperature scarcely changes, but the skin temperature steadily rises, and the patient feels hot.

[1] Barr, D. P., and DuBois, E. F.: Arch. Int. Med., 1918, **21**, 627.
[2] Lusk, G.: Am. J. Physiol., 1910–11, **27**, 427.

Finally there comes a period of falling rectal temperature, the hot blood finds the surface, and there is profuse sweating.

The story is retold in the record of the chart here presented.

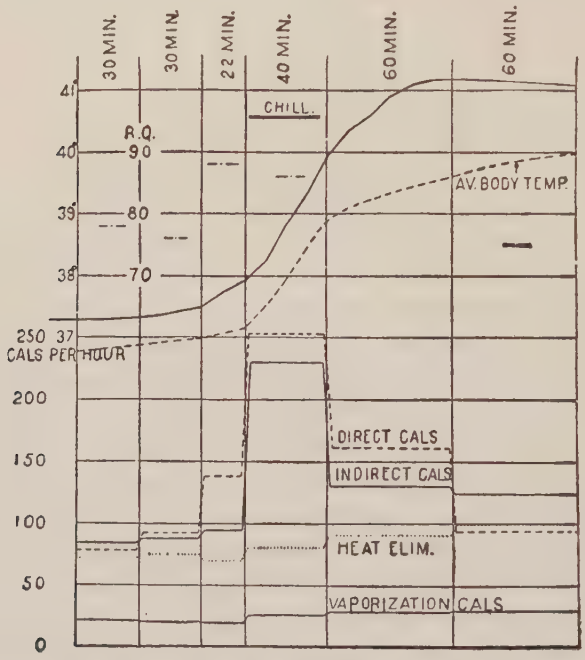


Fig. 41.—Malarial fever. Metabolism chart of George S., March 14, 1917 (Barr and DuBois).

In this investigation it is evident that the rectal temperature is not a criterion of the average body temperature. For the quantity of heat retained in the body, if calculated on the assumption that the temperature of the entire body rose during the chill to the same extent as did the temperature of the rectum, would clearly be too high because the skin temperature was falling at this time. Since the heat determined by indirect calorimetry is a reliable factor, Barr and DuBois deducted from this the quantum of energy lost by radiation and conduction and by evaporation of water. The remainder was the heat stored in the body. On the general assumption that the specific heat of the body is 0.83 (see p. 73), it may be calculated to what average body temperature the heat retained would raise the body. The initial "average body temperature" is assumed to be 0.5° lower than that of the rectum, and the further tracing of the

curve of average body temperature, which is shown on the chart, follows the method above outlined.

Patients with malaria show evidences of negative nitrogen balances despite an ample intake of food. When taking a diet containing 15 gm. of nitrogen there may be a body loss of 1.8 gm. of nitrogen. The patient just described did not come into nitrogen equilibrium until 6 days after his last paroxysm. There is evidently a toxic waste of protein.

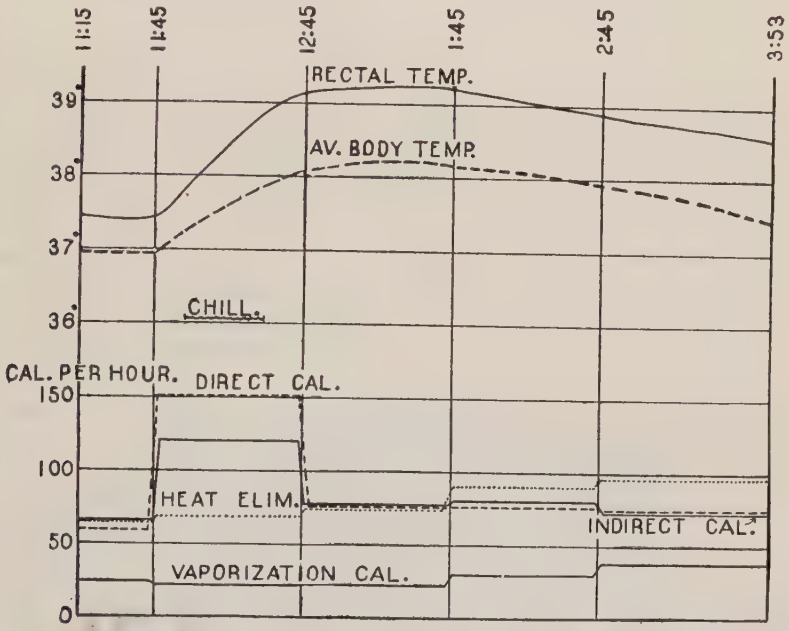


Fig. 42.—Calorimeter observation on Frank G., February 23. At 10:51 a.m. 35 million typhoid bacilli were given intravenously. The chill lasted from 11:58 a.m. to 12:25 p.m. The average body temperature rose less sharply than the rectal temperature (Barr, Cecil, and DuBois).

After treatment with quinine the metabolism returns to the normal basal value. DuBois[1] has imitated this chill in himself in the respiration calorimeter, making movements of shivering and raising his heat production from a rate of about 70 to one of 195 calories per hour, an increase of 180 per cent. This level of heat production, which is comparable with that of 216 per cent. in the malarial patient, caused a rise in the body temperature of only 0.5°. The heat elimination, by both radiation and conduction and by the

[1] DuBois, E. F.: "Basal Metabolism in Health and Disease," Philadelphia, 2d ed., 1927.

evaporation of water, rose to meet the needs for the discharge of heat in this normal individual.

Barr, Cecil, and DuBois[1] have reported results analogous to those found in malarial chill after the injection of foreign protein or of *typhoid vaccine* into man. A curve showing the behavior of the latter is here given. It is especially interesting as it includes the period when, with falling body temperature, the heat elimination exceeds the heat produced, showing the method by which the temperature of the body falls. (Fig. 42.)

TYPHOID FEVER

Pioneer work with accurate technic upon the subject of the respiratory metabolism in typhoid fever was first accomplished by Kraus,[2] Grafe,[3] Rolly,[4] and Coleman and DuBois,[5] but the most complete work upon the subject is presented in the calorimeter studies of Coleman and DuBois. These authors give the following table which shows the correspondence between direct and indirect calorimetry obtained with patients suffering from typhoid:

	Indirect	Direct	Divergence Per Cent.
Total calories measured in all experiments...	12,822.03	12,539.67	−2.2
Excluding first periods.....	8,470.93	8,488.97	+0.2
Calories measured in febrile experiments excluding all first periods.....	5,720.21	5,583.55	−2.4

Ten individuals were investigated. Metabolism records were obtained on sixty-five days. Twenty-four of these were devoted to the study of Morris S., a patient whose metabolism was determined through the course of the fever and two relapses, and one year later when he returned to the hospital in perfectly normal health. This gave the opportunity of contrasting the effect of the specific dynamic action of protein in the same individual in fever and in health.

The results of Coleman and DuBois[6] are presented in the form of a chart (Fig. 43).

In every one of these cases there was a rising body temperature. In every case but one an increase in heat production accompanied the rising body temperature; and the heat elimination, though not

[1] Barr, D. P., Cecil, R. L., and DuBois, E. F.: Arch. Int. Med., 1922, **29**, 608.
[2] Kraus, F.: Z. klin. Med., 1891, **18**, 160.
[3] Grafe, E.: Deut. Arch. klin. Med., 1911, **101**, 209.
[4] Rolly, F.: *Ibid.*, 1911, **103**, 93.
[5] Coleman, W., and DuBois, E. F.: Arch. Int. Med., 1914, **14**, 168.
[6] Coleman, W., and Du Bois, E. F.: *Ibid.*, 1915, **15**, 887.

equal to the heat production, rose to meet the needs of the higher level of metabolism. The major part of the evidence, therefore, points to an increase in the metabolism which is coincident with an elevation of body temperature when determinations are made in

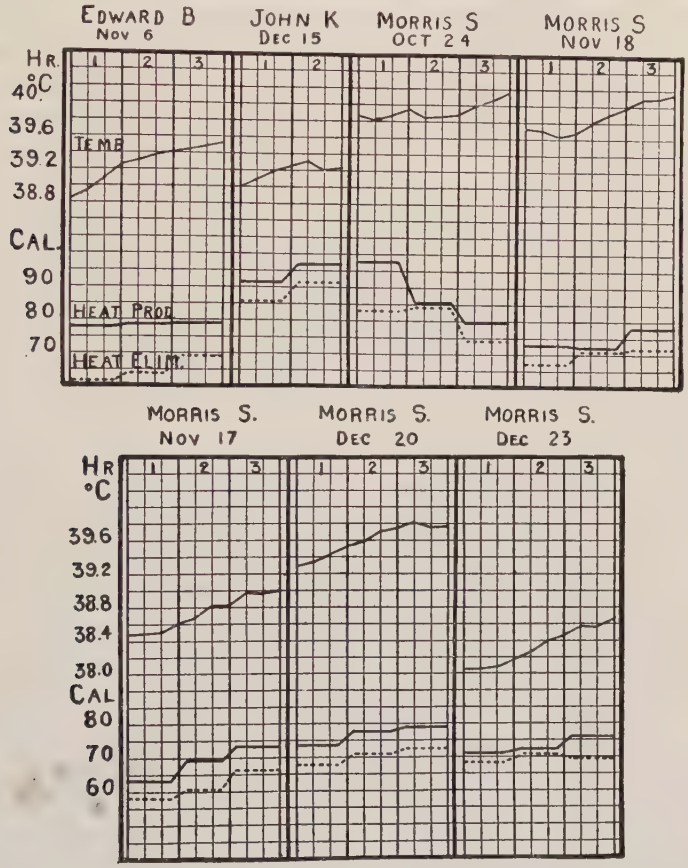


Fig. 43.—Curves showing the relationship and heat elimination in fever. Rising temperature. The uppermost line shows the rectal temperature as measured every twenty minutes. The heavy continued line represents the heat production in hourly periods as determined by the method of indirect calorimetry. The dotted line gives the heat elimination as determined by the measurement of the calories of radiation, conduction, and vaporization. The difference between the levels of these two lines represents the heat stored in the body as the temperature rises. Note the fact that in every case except one the heat elimination increases with a rising temperature.

hourly periods. In one instance (Morris S., October 24th) the heat production and heat elimination both fell notwithstanding a rising body temperature. This could only have been accomplished through an alteration in the apparatus for the elimination of heat from the body, in the sense of Traube's analysis of fever.

Coleman and DuBois also cite experiments which show that when the body temperature is constant in high fever the heat production and heat elimination are equal to each other, and when the body temperature falls the heat elimination rises above the heat production while the amount of the latter may or may not fall.

A remarkable phenomenon is that the percentage of calories lost from the body by the evaporation of water is the same in health and at the levels of increased heat elimination attained in typhoid and in hyperthyroidism. The following comparison is made by Barr, Cecil, and DuBois:[1]

Diagnosis	Metabolism above Normal Basal in Per Cent.	Calories Lost by Vaporization of Water in Per Cent.
1. Typhoid	+41	24
2. Goiter	+39	25
3. Typhoid	+37	23
4. Goiter	+39	22
5. Typhoid	+28	23
6. Goiter	+37	25

Coleman and DuBois state that the average increase in the basal metabolism in typhoid fever is approximately 40 per cent., although figures of over 50 per cent. are frequently encountered. The following table shows the average results obtained during the various weeks of typhoid fever:

BASAL METABOLISM, ACCORDING TO PERIODS OF TYPHOID FEVER

Periods	Number of Patients	Number of Observations	Average Per Cent. Rise above Average Normal 34.7 Calories per Sq. M.	Average Respiratory Quotient
Ascending temperature	2	2	+37	0.79
Continued temperature	5	7	+42	0.77
Early steep curve	3	4	+26	0.82
Late steep curve	3	3	+16	0.82
Relapse—				
Ascending temperature	2	3	+25	0.82
Continued temperature	2	2	+51	0.76
Early steep curve	2	4	+36	0.78
Late steep curve	1	1	+16	0.79
Convalescence—				
First week	3	4	− 2	0.91
Second week	3	5	+ 6	0.88
Third week	1	1	+17	0.81
Fourth week	2	2	+15	0.86
Fifth week	2	2	+ 4	0.81

[1] Barr, D. P., Cecil, R. L., and DuBois, E. F.: Arch. Int. Med., 1922, **29**, 608.

The considerable increase in metabolism during the second, third, and fourth weeks of convalescence is a noteworthy discovery. It is during this period that a regeneration of body protein takes place, and DuBois points out that the heightened metabolism is reminiscent of the increased heat production during the period of growth in childhood.

The specific dynamic action of food administered in typhoid fever was found to be almost negligible, although during convalescence it was as high as in normal individuals. The following table shows these results:

SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER, AND CONVALESCENCE

Subjects	Number of Experiments	Average Gm. of Nitrogen or Glucose in Food	Average Gm. Food per Kg. Body Weight Nitrogen or Glucose	Average Per Cent. Rise in Metabolism
Protein meal				
Two normal men*	2	10.1	0.147	9.3
Four febrile patients	6	8.6	0.174	4.5
Four convalescents	5	10.2	0.217	16.6
Commercial glucose				
Three normal men*	3	115.0	1.6	9.1
Two febrile patients	4	115.0	2.2	1.0
Three convalescents	3	115.0	2.7	9.8

* After the completion of this work two more normal controls received the test-meals. Morris S., on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. N.; Albert G., on Jan. 6, 1915, showed an increase of 9 per cent. in his metabolism after 115 gm. commercial glucose.

The meal containing protein was as large as the patient could be persuaded to take. The results of the ingestion of large amounts of food caused only a slight increase in the basal metabolism during fever, one of 5 per cent. in the case of protein and only 1 per cent. in the case of commercial glucose. The ancient doctrine of "starving a fever" herewith falls to the ground.

The effect of bodily activity upon the basal metabolism does not appear to be as marked during typhoid fever as in health. Thus, Coleman and DuBois describe how Morris S. was quiet during a first hour, was restless and tossed about the bed during a second hour, and during a third hour was evidently irrational, tossed about, wrote several long notes which he held up to the calorimeter window, telling of animals that were biting him with their sharp teeth. Yet his metabolism, which was 43 per cent. above the normal for the three-

hour period, was only 5 per cent. higher than during a quiet period of observation of the basal metabolism made two days later when the body temperature was lower.

The principal cause of the increased metabolism in typhoid fever lies, therefore, in the febrile process itself, and food and restlessness have little influence.

The respiratory quotients were normal, the lowest being 0.72, obtained during fasting, and the highest 1.04, obtained after carbohydrate ingestion.

The large quantities of food administered to the typhoid patients in the "high calorie diet" are as completely absorbed as they would be in health.[1]

TYPHOID FEVER. PROTEIN METABOLISM

Infectious fevers are characterized by a toxic destruction of body protein. Such a toxic action on body protein is also observed in cancerous cases, as was described by Friedrich Müller.[2] He writes: "In the 7 cases (of carcinoma) cited, the nitrogen excretion was larger than the nitrogen ingestion, and consequently the body lost protein. In 2 cases the protein loss was no greater than in healthy individuals with similar insufficient nourishment. In all the other cases the protein metabolism was decidedly above that of healthy men under the same conditions. Even an ample dietary was not able to establish nitrogen equilibrium. As more food was given the nitrogen elimination rose higher and higher, but the point of nitrogen equilibrium seemed unattainable." Müller compared the cachexia of carcinoma with that found in febrile processes and believed them to be analogous.

Under these conditions the heat production may be increased 30 or 40 per cent. above the normal, despite the characteristic cachexia.[3] In milder cases of carcinoma, however, an increase in metabolism is not apparent.[4]

F. Müller[5] reports a daily loss of 10.8 grams of nitrogen (equal to 318 grams of muscle) by a typhoid patient during eight days of fever

[1] DuBois, E. F.: Arch. Int. Med., 1912, **10,** 177; Coleman, W., and Gephart, F. C.: *Ibid.*, 1915, **15,** 882.
[2] Müller, F.: Z. klin. Med., 1889, **16,** 496.
[3] Wallersteiner, E.: Deut. Arch. klin. Med., 1914, **116,** 145.
[4] Magnus-Levy, A.: Z. klin. Med., 1906, **60,** 177.
[5] Müller, F.: Centralbl. klin. Med., 1884, **5,** 569.

when the daily food contained 8.3 grams of protein nitrogen and about 1000 calories. Administration of antipyrin which lowered the body temperature somewhat lessened the protein destruction.

The toxic destruction of protein in infective fever was definitely established by Kocher,[1] who found that after giving to a paratyphoid patient a diet containing carbohydrate in large amount and containing very little protein it was absolutely impossible during the febrile period to reduce the output of urinary nitrogen to that corresponding to the low level of the normal wear and tear quota of protein metabolism. With the decrease in the intensity of the febrile process the loss of body nitrogen gradually diminished. This appears in the following table:

PROTEIN METABOLISM IN PARATYPHOID FEVER
(Weight, 57.5 to 59.8 kgm.)

Day of Fever	Food			N in Excreta, Gm.	N Loss, Gm.	Uric Acid, Gm.	Highest Temp.
	Cal.	N Gm.	Cal. per Kg.				
10	3448	4.7	60	21.09	−16.39	1.38	39.2°
11	3335	4.7	58	18.35	−13.75	1.26	39.3°
12	3213	2.2	56	.....	.....	....	39.3°
13	3213	2.2	56	16.9	−14.7	0.93	38.75°
14	3213	2.2	56	16.46	−14.26	1.23	38.7°
15	3213	2.2	56	15.4	−13.2	1.01	38.45°
16	3213	2.2	56	10.4	− 8.2	0.68	37.3°
17	3213	2.2	56	5.76	− 3.56	0.58	37.6°
18	4666	3.5	78	6.70	− 3.20	0.61	38.1°
19	4666	3.5	78	6.79	− 3.29	0.45	37.1°
20	4666	3.5	78	5.81	− 2.31	0.41	Normal.
21	4666	3.5	78	5.93	− 2.43	0.26	Normal.

Daily creatinin reduced from 2.5 to 1.5 grams.

Although the nitrogen in the urine of a normal man when this diet is given ranges between 2.5 to 4 grams, during the febrile period of this typhoid patient it averaged 16 grams and even reached 20 grams per day. Creatinin, uric acid, sulphur, and phosphorus elimination were increased during the febrile period, but declined with the decline in protein metabolism.

Coleman and DuBois[2] gave to typhoid patients diets which contained much larger quantities of protein (as much as 16 grams of nitrogen daily), but they were unable to obtain nitrogen equilibrium, even though the diet was rich in carbohydrate. The following table gives a summary of their data:

[1] Kocher, R. A.: Deut. Arch. klin. Med., 1914, **115**, 106.
[2] Coleman, W., and DuBois, E. F.: Arch. Int. Med., 1915, **15**, 887.

CHART SHOWING NEGATIVE NITROGEN BALANCES IN TYPHOID PATIENTS WHO RECEIVE FOOD CALORIES IN EXCESS OF CALCULATED HEAT PRODUCTION. RESULTS ARE AVERAGES PER DAY

Patient	Dates or Days of Disease, Inclusive	Days in Period	Range of Maximum Temperature, Degrees F.	Calculated Heat Production, Cal.	Food Calories	Food N, Gm.	Nitrogen Balance, Gm.
Morris S...	Oct. 23–Nov. 3	12	102.8–104.6	2266	2863	16.4	−4.4
	Dec. 19–24	6	101.9–105.1	2085	2989	13.2	−2.4
Charles F..	Nov. 28–30	3	101.2–103.4	1752	2458	12.0	−4.6
Karl S.....	Jan. 12–18	7	101.0–105.0	2197	2985	16.1	−3.2
	Jan. 19–22	4	98.8– 99.0	1678	2819	14.6	−1.9
John K....	Jan. 15–20	6	103.2–104.0	2568			
	Days of Disease						
Frank W..	11–14	4	104.0–105.4	2200	2250	11.3	−5.0
	15–19	5	103.0–104.0	2238	3320	15.3	−3.3
	20–23	4	101.0–103.6	2054	2362	15.9	−1.5

Coleman and DuBois conclude that, though there was ample protein in the diet to establish nitrogen equilibrium in the normal man, it could not accomplish this in typhoid fever. It was impossible to escape the conclusion that the destruction of protein is caused by the toxins of the disease. In some cases the protein destruction continued several days after the body temperature had reached a low level.

TYPHOID FEVER. HIGH CALORIE DIET

The experiments of von Hösslin[1] strongly affirmed the beneficence of a liberal diet in ordinary fevers. He writes: "The results show that febrile patients, or at least those who do not run temperatures above 40° to 40.5°, can digest and absorb the total amount of protein, fat, and carbohydrates which can be given them with their diminished appetite, provided the food is administered in a proper form. Temperature and metabolism are only slightly increased thereby."

The efficiency of a carbohydrate diet in typhoid fever was first demonstrated by Shaffer and Coleman,[2] who showed that the ingestion of large amounts of carbohydrate in a medium protein diet may almost maintain the patient in nitrogen equilibrium throughout the disease. The diet consisted of milk, milk-sugar, diluted cream, eggs, and sometimes arrow-root starch. Shaffer writes: "It was only when we gave 60, 70, or even 80 calories per kilogram of body weight

[1] von Hösslin, H.: Virchow's Arch. path. Anat., 1882, **89,** 317.

[2] Shaffer, P. A.: J. Am. Med. Assn., 1908, **51,** 974; Shaffer, P. A., and Coleman, W.: Arch. Int. Med., 1909, **4,** 538.

—between 3000 and 4000 calories—that the greatest sparing was observed."

The results obtained from two individuals suffering from typhoid are presented in the following table:

INFLUENCE OF CARBOHYDRATES ON PROTEIN METABOLISM IN TYPHOID FEVER

Period	No. of Days in Period	Range of Maximum Temp. during Period	Total Calories of Food	Calories per Kg.		Nitrogen in Food Gm.	Nitrogen to Body
				Total	From Carbohydrates		
Subject I.							
I.....	4	104 –103.2° F.	4280	72	48.0	13.9	− 0.9
II.....	6	103.6–102.8° F.	5200	85	48.0	15.0	− 0.2
III.....	4	103.8–103.4° F.	2750	45	7.0	15.0	− 8.5
IV.....	8	104.8–101.4° F.	5340	89	52.0	14.5	− 2.8
V.....	6	100.8– 99.4° F.	4990	83	48.0	13.8	+ 1.2
VI.....	4	Normal.	2430	41	7.0	13.5	− 0.3
Subject II.							
I.....	9	104.4–102.6° F.	1920	31	7.8	12.6	−11.3
II.....	6	102.8–100.6° F.	4290	70	47.0	12.6	− 1.1*
III.....	6	Normal.	1930	32	8.0	12.7	− 3.8
IV.....	8	102.8– 99.6° F. Relapse.	4800	78	50.0	14.1	+ 3.6
V.....	6	Normal convalescence.	2460	39	12.0	14.6	+ 1.8

* Average for last three days of diet.

From this it may be concluded that nitrogen equilibrium may be very nearly maintained throughout the course of typhoid fever on a diet containing 12 to 15 grams of nitrogen, provided an excess of carbohydrate beyond the requirement of the organism be also administered. Upon this basis rests the very notable advance achieved by the Coleman-Shaffer "high calorie diet." It is unknown to what extent a diet high in fat and low in carbohydrate would affect the protein metabolism in fever.

ERYSIPELAS

Riethus[1] found an increase of 41 per cent. in metabolism in erysipelas, and Grafe,[2] in a patient with a temperature of 39.5°, found a 40 per cent. increase in metabolism above that shown by the same man after recovery.

[1] Riethus, O.: Arch. exper. Path. u. Pharm., 1900, **44**, 239.
[2] Grafe, E.: Deut. Arch. klin. Med., 1910–11, **101**, 209.

Kocher[1] gave to four erysipelas patients diets containing 3200 to 4300 calories and only 1.8 to 2.2 gm. of nitrogen. While normal men excrete from 2 to 4 gm. of nitrogen in the urine when they partake of such diets, the nitrogen excretion of the erysipelas patients runs between 9 and 20 gm. daily. This indicates a profound toxic waste of tissue.

Coleman, Barr, and DuBois[2] studied eight cases in the respiration calorimeter. In the sum of their measurements of metabolism they found 2153 calories directly measured and 2,119 calories by indirect calorimetry, a difference of 1.1 per cent. During the course of the fever the metabolism was always high, varying between 19 and 40 per cent. above the normal. At a body temperature of 40° the basal metabolism was 40 per cent. above the normal. No specific differences were to be noted between the metabolism of erysipelas and of typhoid fever; in both the heat production rises with the body temperature and in both there is a greatly increased protein metabolism due to toxic processes acting on tissue. The authors state that on account of lack of coöperation due to the mental state of the patients, erysipelas was a disappointment from an experimental standpoint.

PNEUMONIA

During fever in croupous pneumonia the protein metabolism is much higher than normal. After the crisis there is still a large excretion of nitrogen in the urine which continues until the croupous exudate has been decomposed by autolysis, absorbed by the blood, and metabolized in the body (epicritical nitrogen elimination). In acute pneumonic phthisis (galloping consumption), with its caseous transformation of lung tissue, there is a very high waste of tissue protein. Friedrich von Müller[3] has shown that while the croupous exudate readily undergoes autolysis at a temperature of 40°, with the production of deutero-albumoses, lysin, leucin, tyrosin, etc., the caseous mass does not undergo autolysis, although it permits free diffusion of soluble material, such as phosphates. Hence, although the protein of the cheesy mass is insoluble in the organism, the soluble toxins may be absorbed from the diseased part, and be the causative agent of the rapid destruction of body protein in galloping consumption.

[1] Kocher, R. A.: Deut. Arch. klin. Med., 1914, **115,** 82.
[2] Coleman, W., Barr, D. P., and DuBois, E. F.: Arch. Int. Med., 1922, **29,** 567.
[3] von Müller, F.: Verhandl. xx Congresses für innere Medizin, 1902, section iv, p. 192.

An illustration of the course of nitrogen metabolism in pneumonia may also be taken from von Leyden and Klemperer.[1] The details with values in grams are given below:

METABOLISM IN PNEUMONIA

Temp. on Successive Days	Food					Excreta			Loss of Body N
	Quantity in Grams	Calories	N	Fat	Carbohydrates	Urine N	Feces N	Total N	
40.8 (highest).	2000 milk.	1360	10.6	70	90	24.7	0.9	25.6	15.0
40.9 (highest).	2000 milk, 150 cream, 100 lactose.	1980	11.4	85	197	22.8	0.9	23.7	12.3
41.2 at 12 M. 36.8 at 7 P. M.	2000 milk, 150 lactose.	1975	10.6	70	240	21.7	0.9	22.6	12.0
37.3 (highest).	2000 milk, 200 cream.	1612	11.7	90	99	21.9	1.1	23.0	11.3
36.8 (highest).	2000 milk, 200 cream, 2 eggs.	1752	13.7	100	99	18.5	1.1	19.6	5.9
36.8 (highest).	2000 milk, 300 cream, 4 eggs.	2018	17.3	120	104	18.7	1.1	19.8	2.5

In this case it is apparently demonstrated that nitrogen equilibrium cannot be obtained during high fever, and also that the loss of body nitrogen does not cease at the crisis, but rather continues on account of the epicritical elimination of nitrogen derived from the protein of the croupous exudate. During the time of this epicritical elimination the body appears unable to add new protein to itself. About four days after the crisis true convalescence begins, with the upbuilding of new protein tissue.

On account of coughing and dyspnea in patients severely ill with pneumonia, this disease has never been studied with the respiration calorimeter. DuBois[2] states that in a few investigations by Kraus,[3] Riethus,[4] Svenson,[5] Grafe,[6] and Rolly[7] the basal metabolism has been found to be 20 to 50 per cent. above the normal (in one case 70 per cent. above), or increases similar to that found in typhoid fever.

Ever since the experiments of von Leyden[8] a retention of water in fever has been assumed. It has also been shown that there is a

[1] von Leyden, E., and Klemperer, G.: "Handbuch der Ernährungstherapie," Leipzig, 1904, **2**, p. 345.

[2] DuBois, E. F.: "Basal Metabolism in Health and Disease," Philadelphia, 2d ed., 1927, p. 391.

[3] Kraus, F.: Z. klin. Med., 1891, **18**, 160.

[4] Riethus, O.: Arch. exper. Path. u. Pharm., 1900, **44**, 239.

[5] Svenson, N.: Z. klin. Med., 1901, **43**, 86.

[6] Grafe, E.: Deut. Arch. klin. Med., 1911, **101**, 209.

[7] Rolly, F.: *Ibid.* 1911, **103**, 93.

[8] von Leyden, E.: *Ibid.* 1868–69, **5**, 273.

retention of sodium chlorid within the body. The intimate relation between the retention of water and salt has been beautifully demonstrated by Sandelowsky[1] in Lüthje's clinic. Thus, during the period of high fever in pneumonia a gain in weight, a sodium chlorid retention, and a dilution of the organic contents of the blood usually went hand in hand. After the crisis, however, a loss in weight, a loss of chlorid, and a greater concentration of blood resulted. Similar conditions were found in scarlet fever.[2] Sandelowsky observed that when sodium chlorid was given to a patient convalescent from pneumonia it was not so readily eliminated by the kidney as it would have been normally. He attributed this to a disturbed renal condition which was not wholly restored to the normal after the crisis. This brought about sodium chlorid retention, which in turn caused water retention, that the normal osmotic conditions might be preserved, thus accounting for the gain in body weight and the loss in the concentration of the blood in fever.

It has since been shown that failure to excrete chlorid during the acute stage of the disease is almost always associated with a concentration of sodium chlorid in the blood-plasma below 5.62 grams per liter, which is the normal threshold value of excretion[3] (see p. 201). Hence the retention of sodium chlorid is not due to kidney insufficiency.

TUBERCULOSIS

The metabolism in tuberculosis has been described by McCann and Barr[4] in an article which gives an admirable history of the subject, which history need not here be recorded. McCann and Barr studied fifteen cases. The surface area of each patient was determined by the Height-Weight formula of DuBois. From the Aub-DuBois standards of predicting the basal metabolism those of Harris-Benedict differed by an average variation of 3 per cent.

In the determination of the basal respiratory quotient an average of 0.79 shows nothing abnormal.

In ten of the fifteen patients, when the temperature was normal, the metabolism was +3 to +15 per cent. above the normal. Perhaps the true level is still higher, for normal people emaciated to the

[1] Sandelowsky, J.: Deut. Arch. klin. Med., 1909, **96**, 445.
[2] Oppenheimer, S., and Reiss, E.: *Ibid.*, p. 464.
[3] Snapper, J.: *Ibid.*, 1913, **111**, 429; McLean, F. C.: J. Exp. Med., 1915, **22**, 366.
[4] McCann, W. S., and Barr, D. P.: Arch. Int. Med., 1920, **26**, 663.

degree of tuberculous patients have a lowered basal metabolism. When the tuberculous patient has a febrile temperature the metabolism rises. Thus in one instance, with a body temperature of 40° the basal metabolism was +29 per cent. above the normal basal level. This is a customary rise for that body temperature.

After administering a meal consisting of 350 gm. of meat and 10 gm. of butter containing 547 calories the specific dynamic action was the same in the tuberculous as in the normal man, to which the following table bears witness:

SPECIFIC DYNAMIC ACTION OF MEAT
(Increase over basal in per cent.)

Hour after Food	Normal Men	Tuberculosis	
		Average	Maximum
2	+16	+16	+31
3	+24	+18	+25
4	+24		
	+21	+17	

McCann and Barr find that neither the food nor the protein requirement is large for tuberculous patients. They may be maintained with 2000 calories and are in nitrogen equilibrium with 10 gm. of protein nitrogen given daily. The toxic waste of protein is not large. Forced feeding is unnecessary and probably harmful. Since protein and carbohydrate increase the metabolism and therefore the respiratory activity in the tuberculous to the same extent that it does in normal persons, it was suggested that their intake be limited during periods when the disease is active in order to put the lungs at rest.

In two important papers McCann[1] subsequently elaborated this analysis. The larger pulmonary ventilation in patients with tuberculosis is thus portrayed:

Number of Subjects		Number of Respirations per Min.	Volume of Respirations in C.C. per Min.	CO_2 Eliminated in C.C. per Min.	Ratio, Min. Vol. to CO_2 per Min.
5	Normal	11	4255	167	25.9
5	Tuberculous	25	8249	195	42.5

The influence of food upon the activity of the respiration of these subjects may be compared as follows:

[1] McCann, W. S.: Arch. Int. Med., 1921, **28**, 847; 1922, **29**, 33. In the latter article one may read a fine discussion of the nitrogen minimum in disease.

	Food, Gm.	Change in Metabolism, Per Cent.	Change in Ventilation, Per Cent.
Normal	Protein, 73	+40	+40
Tuberculous	Protein, 73	+29	+25
Normal	Protein, 31	+ 3	± 0
Tuberculous	Protein, 21	−11	− 5
Tuberculous	Fat, 140	+12	+14.5
Tuberculous	Glucose, 100	± 0	+17

A small quantity of protein exerted no specific dynamic action and did not increase the ventilation of the lungs. But 100 gm. of glucose, containing 375 calories, though it failed to increase the metabolism, yet through its combustion increased the volume of carbon dioxid to be eliminated and it raised the ventilation of the lungs 17 per cent. Moreover, 140 gm. of fat, containing 1312 calories, though it raised the heat production 12 per cent., caused an increase in the ventilation of the lungs of only 14.5 per cent. It is obvious that nutriment introduced in the form of fat, with little carbohydrate, together with a low protein intake, constitutes a rational diet for the man ill with pulmonary tuberculosis.

As regards the protein requirement, McCann compares the low levels of protein metabolism, as determined by Sivén[1] and by Kocher[2] upon normal men, with those found in his own studies upon two cases of tuberculosis and finds that there is no inherently large wear and tear quota in this disease. A minimum of 2.5 gm. of urinary nitrogen was obtained in Case 6.

COMPARISON OF PROTEIN METABOLISM IN NORMAL AND TUBERCULOUS MEN

	Length in Days	Day of Experiment	Food	Body Wt.	N in Gm.			±N to Body
					Food	Urine	Feces	
			Cals.	Kg.				
Normal (Sivén)	43	42	2441	58.9	2.43	1.78	1.33	−0.74
Normal (Kocher)	10	5	5089	79.2	1.01	2.92	1.16	−3.07
Tuberculosis (Case 6)	54	9	3012	57.1	3.1	4.5	0.9	−2.3
(" 5)	30	28	3574	46.7	7.2	3.6	1.8	+1.8

As the result of his investigations McCann finds that nitrogen equilibrium may be established when the diet contains 37 to 44 gm. of protein (one-half being from animal sources) and when the calories

[1] Sivén, V. O.: Skan. Arch. Physiol., 1900, **10**, 91.
[2] Kocher, R. A.: Deut. Arch. klin. Med., 1914, **115**, 82.

amount to twice the basal value. He recommends that the hospital diet contain 2500 calories, with 60 to 90 gm. of protein for the tuberculous patient. A greater number of calories is required if the individual is capable of mechanical work.

The important conception of Rubner concerning the wear and tear quota of protein metabolism has been of signal service in interpreting the toxic waste of protein in disease. This aspect has been capably investigated by Lauter and Jenke[1] in Friedrich von Müller's clinic, with results similar to the American work on the subject.

In all fevers the septic products act upon the hunger centers of the brain and appetite is wanting. This is in evidence throughout the course of tuberculosis and tends to weaken the body's resistance through undernutrition. It is therefore desirable at all times to maintain the nutritive condition of the patient.

METABOLISM IN FEVER AND VAN'T HOFF'S LAW

DuBois, in his "Metabolism in Health and Disease," calls attention to the remarkable parallelism in fever between the body temperature and the height of the total metabolism. Notwithstanding the dissimilarity of the various infective processes, the height of the basal metabolism is closely proportional to the body temperature. The higher temperature speeds the velocity of chemical reactions.

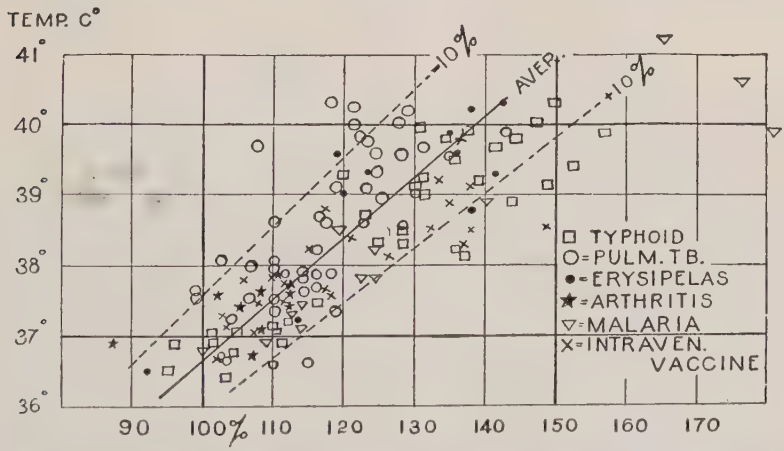


Fig. 44.—Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10 per cent. above and 10 per cent. below the average. (Reproduced by permission from E. F. DuBois' "Basal Metabolism in Health and Disease," Lea & Febiger, Philadelphia, 2d ed., 1927, p. 390.)

[1] Lauter, S., and Jenke, M.: Deut. Arch. klin. Med., 1925, **146**, 323.

Van't Hoff's Law reads, "With a rise in temperature of 10° C., the velocity of chemical reactions increases between two and three times. In other words the coefficient is between 2 and 3."

DuBois has plotted the increase in the rate of metabolism, contrasting it with the height of body temperature, and finds the average coefficient in fevers of all kinds to be 2.3. The values obtained run within a plus or minus error of 10 per cent. Van't Hoff's chart showing the influence of temperature upon chemical reactions, such as may take place in test-tubes, is given by DuBois in contrast with his own upon the influence of temperature upon the chemical reactions in fever, and the two are here reproduced (Figs. 44 and 45).

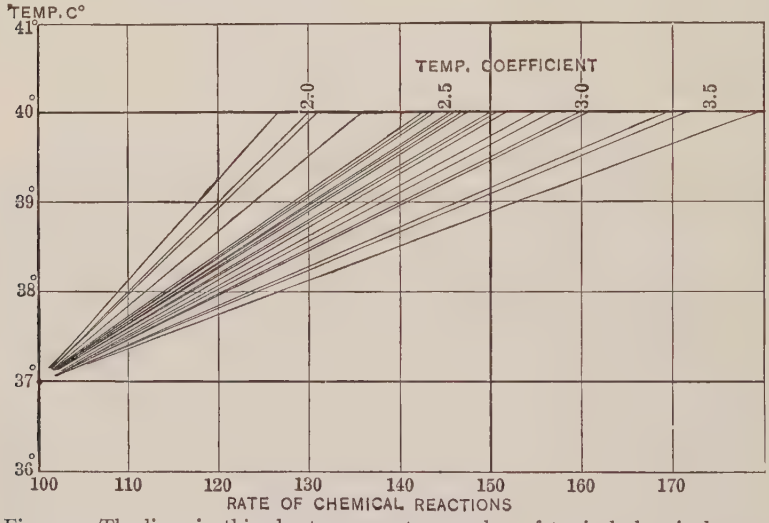


Fig. 45.—The lines in this chart represent a number of typical chemical reactions from van't Hoff and Kanitz. The slant of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body. (Reproduced by permission from E. F. DuBois's "Basal Metabolism in Health and Disease," Lea & Febiger, Philadelphia, 2d ed., 1927, p. 391.)

Matters are so shaping themselves at this writing that it seems probable that the Russell Sage Institute of Pathology may not long be continued in its present form. It may be of interest to note that it was established for work in 1912 in two small rooms of the Second (Cornell) Medical Division of Bellevue Hospital, a municipal hospital, where it built the respiration calorimeter and has maintained a corps of workers for over fifteen years upon an annual budget of $12,000 to $16,000.

CHAPTER XXIX

PURIN METABOLISM—GOUT

"Was ist die wissenschaftliche Wahrheit? Ein Irrtum von heute."

Uric acid was discovered in urinary calculi by Scheele in 1779, and was found to be present in gouty concretions by Wollaston in 1797. It has since been the subject of investigations almost without number, and of theoretic speculation beyond that of any other chemical substance described in medical literature. The older work concerning the excretion of uric acid is almost valueless on account of the inadequacy of the chemical methods of the times. Accurate determinations of uric acid date from the introduction of a new method of analysis by Salkowski in 1882, and of allantoin by Wiechowski in 1908.

The newer researches are also based on more exact chemical knowledge of the precursors of uric acid. Much valuable information has been gathered as regards the normal method of production of uric acid, although it will be seen that on the pathologic side there is little beyond the conjectural to reward the student.

THE CHEMICAL ANATOMY OF THE PURINS

Emil Fischer[1] grouped together uric acid, hypoxanthin, xanthin, adenin, and guanin as bodies whose varying structure depended upon slight changes around the chemical nucleus of a substance called purin. Purin, according to Fischer, may occur in the body, but on account of its ready decomposability, has not been discovered there.

The relations between the purin bodies may be judged from the following formulæ.

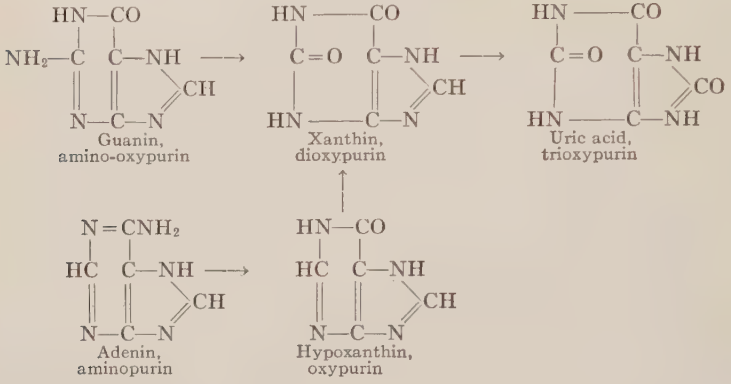
Purin	$C_5H_4N_4$
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Uric acid	$C_5H_4N_4O_3$
Adenin	$C_5H_3N_4NH_2$
Guanin	$C_5H_3N_4ONH_2$

Hypoxanthin, xanthin, and uric acid are respectively mono-, di-, and tri-oxypurin. Adenin is aminopurin, and guanin is aminohypo-

[1] Fischer, E.: Ber. deut. chem. Gesellsch., 1899, **32**, 435.

xanthin. It is evident that uric acid is the most highly oxidized product of the series, and might readily arise from the oxidation of hypoxanthin and xanthin. It is also apparent that by supplanting the NH_2 group in adenin and guanin by O, they would be converted into hypoxanthin and xanthin respectively, and that from these substances uric acid might arise through oxidation.

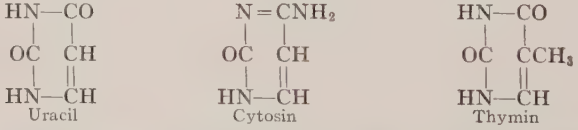
These reactions may be thus expressed:



The deamination of guanin and adenin is accomplished by hydrolysis and may occur in the absence of oxygen, whereas the conversion of hypoxanthin into xanthin and the latter into uric acid are true processes of oxidation.

The knowledge of the hydrolytic cleavage products of nucleic acid is derived largely from the work of Kossel,[1] who added adenin, cytosin and thymin to chemical literature.

The formulæ of the three pyrimidin bases—uracil, cytosin, and thymin—are as follows:



Kossel and Steudel[2] point out the fact that purin bases contain the pyrimidin nucleus, and that cytosin, for example, needs only cyanic acid, CONH, and an atom of oxygen to convert it into uric acid.

[1] For the extensive literature on this subject consult the valuable monograph of Walter Jones, "Nucleic Acids," 2d ed. London, 1920.

[2] Kossel, A., and Steudel, H.: Z. physiol. Chem., 1903, **38**, 49.

They query whether the pyrimidin bases are precursors or metabolized products of the purins, but the question is still unsettled.[1]

Mendel and Myers[2] report that the pyrimidin bases, when administered intravenously or *per os*, reappear in the urine unchanged without increasing either the purin or the urea output. Deuel,[3] working in Mendel's laboratory, reports that when thymin and uracil are given to dogs in large quantity (1 to 3 gm.) a considerable amount may be recovered in the urine, but when given in small subdivided doses over a period of days none was recoverable. A detectable increase in urea led to the conclusion that free pyrimidins could be oxidized.

Kossel's work presents the following substances as characteristic cleavage products of animal and vegetable nucleic acids:

Animal	Vegetable
Thymus nucleic acid:	*Yeast nucleic acid:*
Phosphoric acid	Phosphoric acid
Guanin	Guanin
Adenin	Adenin
Cytosin	Cytosin
Thymin	Uracil
Hexose	Pentose

Bang[4] extracted from the pancreas a nucleic acid containing phosphoric acid, a pentose and guanin, which compound he called "guanylic acid." The presence of a pentose in animal nucleic acid is an anomaly. Levene and Jacobs[5] discovered the formula of guanylic acid, and solved the long-sought problem of the composition of nucleic acid. They submitted guanylic acid to neutral hydrolysis under pressure, which removed phosphoric acid and left a substance (guanosin) which readily broke up on acid hydrolysis into d-ribose and guanin.

These two hydrolyses may thus be written:

$$\begin{matrix} HO \\ O=PO \\ HO \end{matrix}\!\!\diagdown\!\!\diagup\!\!-C_5H_8O_3-C_5H_4N_5O + H_2O = H_3PO_4 + C_5H_9O_4-C_5H_4N_5O$$

Guanylic acid — Guanosin

$$C_5H_9O_4-C_5H_4N_5O + H_2O = C_5H_{10}O_5 + C_5H_5N_5O$$

Guanosin — d-Ribose — Guanin

[1] Consult Abderhalden, E.: "Lehrbuch der physiologischen Chemie," Berlin and Vienna, 1909, p. 381.

[2] Mendel, L. B., and Myers, V. C.: Am. J. Physiol., 1910, **26**, 77.

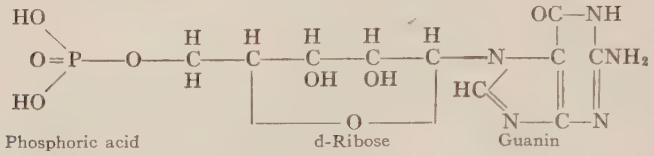
[3] Deuel, H. J., Jr.: J. Biol. Chem., 1924, **60**, 749.

[4] Bang, I.: Z. physiol. Chem., 1898–99, **26**, 133.

[5] Levene, P. A., and Jacobs, W. A.: Ber. d. d. chem. Ges., 1909, **42**, 2469; J. Biol. Chem., 1912, **12**, 421.

Guanylic acid is a monobasic *nucleotid* which yields on cleavage phosphoric acid and the *nucleosid*, guanosin.

Its complete formula[1] is as follows:

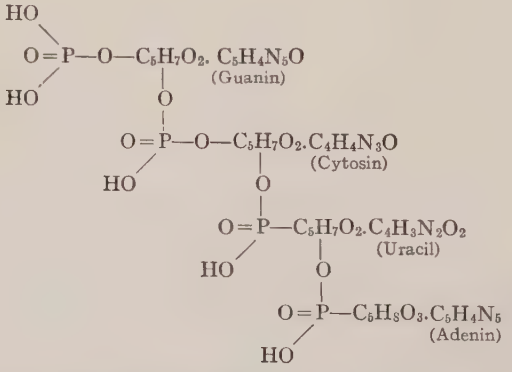


If mild acid hydrolysis be employed guanylic acid breaks up into pentose phosphate and guanin.

Buell and Perkins[2] describe an easy and certain method by which crystals of guanin nucleotid (guanylic acid), having the formula $C_{10}H_{14}N_5PO_8 + 2H_2O$, may be obtained.

Thannhauser[3] was the first to isolate in crystalline form a purin nucleotid when he prepared crystals of adenin nucleotid (or adenosin phosphoric acid, as he called the substance).

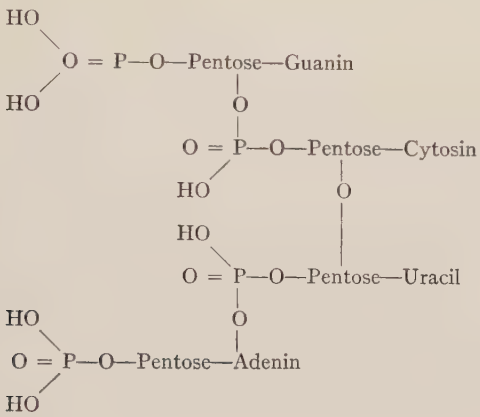
Levene's discovery of the composition of guanylic acid led him to the conclusion that, since four bases, guanin, adenin, cytosin, and thymin, could be recovered from the nucleic acid of the thymus, the formula for nucleic acid might be written as that of a tetra-nucleotid.[4] His definitive formula for nucleic acid was published later.[5] That for yeast nucleic acid is as follows:



[1] Levene, P. A., Yamagawa, M., and Weber, I.: J. Biol. Chem., 1924, **60**, 693.
[2] Buell, M. V., and Perkins, M. E.: *Ibid.*, 1927, **72**, 21.
[3] Thannhauser, S. J.: Z. physiol. Chem., 1919, **107**, 157.
[4] Levene, P. A., and Jacobs, W. A.: J. Biol. Chem., 1912, **12**, 411.
[5] Levene, P. A.: *Ibid.*, 1919, **40**, 415.

This formula is based upon the belief that ester linkages unite the nucleotids. Levene conceives that a kindred structure belongs to thymus nucleic acid.

Jones and Perkins[1] defend a slightly different formula which involves an ether linkage between the two carbohydrate radicles in the middle of the formula given above, thus:



Jones and Perkins disclaim attaching significance to the order or even to the number of the nucleotid groups. In advancing this formula Jones[2] withdrew from his former position that the linkages between the nucleotids were all ether combinations of the carbohydrate groups.

Further study convinced Jones and Perkins[3] that uracil nucleotid was not really present in yeast nucleic acid and was merely the result of the hydrolytic deamination of cytosin nucleotid, thus confirming the suggestion of Kowalevsky[4] that there were only three nucleotids present. Calvery,[5] of Jones's laboratory, has been able to obtain from yeast nucleic acid crystals of guanin, adenin, and cytosin nucleotids, but finds no evidence of the existence of uracil nucleotid. This supports the discovery of Thannhauser of a trinucleotid containing adenin, guanin, and cytosin (see p. 729).

[1] Jones, W., and Perkins, M. E.: J. Biol. Chem., 1923, **55**, 557, 567.
[2] Jones, W.: Am. J. Physiol., 1920, **52**, 193.
[3] Jones, W., and Perkins, M. E.: J. Biol. Chem., 1924–25, **62**, 557.
[4] Kowalevsky, K.: Z. physiol. Chem., 1910, **69**, 240.
[5] Calvery, H. O.: J. Biol. Chem., 1927, **72**, 27.

Selecting the nucleotids forming yeast nucleic acid, one may present this summary of their transformation:

Nucleotids minus H_3PO_4 =	*Nucleosids* minus d-ribose =	*Bases.*
Adenylic acid	⟶ Adenosin	⟶ Adenin
Guanylic acid	⟶ Guanosin	⟶ Guanin
Cytodin-nucleotid	⟶ Cytidin	⟶ Cytosin
Uridin-nucleotid	⟶ Uridin	⟶ Uracil

This is the simplest picture of the transformations which take place. Amberg and Jones[1] have shown that the deaminizing enzymes (see p. 730) may convert guanosin into *xanthosin*, which yields xanthin on hydrolysis, or convert adenosin into *inosin*, which yields hypoxanthin on hydrolysis.

Although Levene has determined that the carbohydrate radicle of plant nucleic acid, such as that in yeast, is d-ribose and that this is also the carbohydrate of guanylic and inosinic acids found in animal tissue, yet the component "hexose" of such a characteristic nucleic acid as that from the thymus remains unknown. It yields levulinic acid on decomposition, and hence it is believed to be a hexose. However, Levene and Sobotka[2] report that the sugar in adenin hexoside, a substance which is separable from yeast and yields levulinic acid, is in reality a methyl keto-pentose containing sulphur and having the following formula:

The true nature of the "hexose" in animal nucleic acid remains undetermined.

ACTION OF ENZYMES

Horbaczewski[3] was the first to note that the ingestion of nucleoproteins largely increased the uric acid in the urine. Food free from nucleoproteins has not this effect. He also found that if fresh spleen pulp, which contains no uncombined purin bases, be permitted to putrefy, xanthin and hypoxanthin made their appearance. If now the pulp was shaken in the air, uric acid was formed from the oxidation of the bases.

[1] Amberg, S., and Jones, W.: Z. physiol. Chem., 1911, **73,** 407.
[2] Levene, P. A., and Sobotka, H.: J. Biol. Chem., 1925, **65,** 551.
[3] Horbaczewski, J.: Sitzungsber. Wiener Acad. Wissenschaft, 1891, **100,** Pt. 3, p. 78.

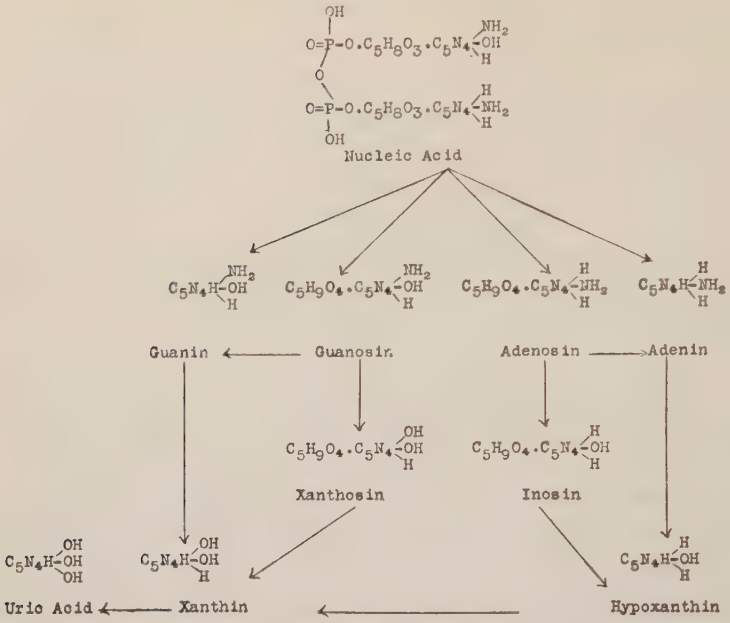
Spitzer[1] found that when air was passed through aqueous extracts of spleen and liver digested at 40°, and with exclusion of putrefaction, uric acid was produced. The quantity of purin bases present decreased with the increased formation of uric acid. Purin bases added to such a digest were converted into uric acid, hypoxanthin, and xanthin readily and almost completely, and guanin and adenin with greater difficulty. This work established the presence of oxidizing enzymes, the xanthin oxidases, which could act on the purin bases in the organism, converting them into uric acid.

Levene and Medigreceanu[2] found that animal ferments have the power of hydrolytic cleavage over nucleic acid. Thus, pancreatic juice or intestinal juice through *nucleinase* (1) causes the resolution of a *polynucleotid* into *mononucleotids*. Animal tissues were also found to contain a similar ferment. Extracts of the mucosa of the intestine contained *nucleotidase* (2) which splits the nucleotids into phosphoric acid and *nucleosids*. The purin nucleosids are broken up by *nucleosidase* (3) into their constituent carbohydrate and purin groups. The pyrimidin nucleosids undergo a similar fate.[3] The kidney, heart muscle, and liver contain all the above-named enzymes, and are, therefore, capable of demolishing the complex molecule of nucleic acid.

The enzyme nucleinase which breaks the polynucleotid complex of nucleic acid may not act as a simple unit. Thus, Jones and Richards[4] found that when the tetranucleotid, yeast nucleic acid, was mixed with pig's pancreas it is split into two dinucleotids; one containing the guanin and cytosin groups, the other, the adenin and uracil groups. Levene[5] however was unable to isolate the adenin-uracil dinucleotid. Not only this, but Thannhauser[6] found that after digesting yeast nucleic acid with human duodenal juice, there remained a trinucleotid containing guanin, adenin, and cytosin. (See p. 727.) Various places of attack are therefore open.

Jones[7] presents the following scheme of the methods of breakdown of a guanin-adenin dinucleotid:

[1] Spitzer, W.: Pflüger's Arch. gesam. Physiol., 1899, **76,** 192.
[2] Levene, P. A., and Medigreceanu, F.: J. Biol. Chem., 1911, **9,** 389.
[3] Deuel, H. J., Jr.: *Ibid.*, 1924, **60,** 749.
[4] Jones, W., and Richards, A. E.: *Ibid.*, 1914, **17,** 71.
[5] Levene, P. A.: *Ibid.*, 1918, **33,** 425.
[6] Thannhauser, S. J.: Z. physiol. Chem., 1914, **91,** 329; 1915, **95,** 259; 1923, **131,** 296.
[7] Jones, W.: "Nucleic Acids," London, 1914, p. 77.



Thannhauser and Ottenstein,[1] following the classical experiments of Horbaczewski, have digested guanosin, adenosin, and xanthosin with liver extracts in the presence of oxygen gas. Such digests yield xanthin or uric acid but never guanin and adenin. The authors believe that the sugar union with purin breaks up at the time of oxidative deaminization and perhaps in consequence of it. This confirms the belief that the free amino purins, adenin and guanin, do not appear in intermediary metabolism.

In the formula given above guanosin would pass through xanthosin into xanthin; and adenosin through inosin into hypoxanthin.

The original investigations of Horbaczewski have been considerably extended by Schittenhelm and notably by Walter Jones, especially in regard to their explanation along lines of enzymotic activity.

Jones and Partridge[2] find that although the great majority of the organs of the body, when self-digested at 40° (autolysis), convert guanin and adenin into xanthin and hypoxanthin, presumably through the action of enzymes, extracts of the spleen of the pig cannot convert guanin into xanthin, although they can convert adenin into hypoxanthin. Jones therefore concludes that an enzyme,

[1] Thannhauser, S. J., and Ottenstein, B.: Z. physiol. Chem., 1921, **114**, 17.

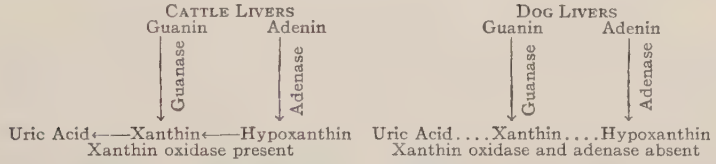
[2] Jones, W., and Partridge, C. L.: *Ibid.*, 1904, **42**, 343; see also Levene, P. A., Am. J. Physiol., 1904–05, **12**, 276.

guanase, which normally removes the NH_2 group and replaces it with O, is wanting in the pig's spleen, while adenase, the enzyme acting on adenin in a similar fashion, is present there. Such a reaction would read:

$$\underset{\text{Adenin}}{C_5H_3N_4NH_2} + H_2O = \underset{\text{Hypoxanthin}}{C_5H_4N_4O} + NH_3$$

Investigating the subject further, the authors found that the pancreas contained the enzyme, guanase, which converts guanin into xanthin.

The behavior of the livers of different animals has been investigated by Jones and Austrian.[1] In cattle livers, for example, adenase, guanase, and xanthin oxidase are present, whereas in dog livers guanase is present, adenase occurs in traces only, and no xanthin oxidase whatever has been found. Hence cattle livers may form uric acid from adenin and guanin, while dog livers only convert guanin into xanthin and the other processes are arrested. The process is thus graphically represented:



Furthermore these authors find that the guanase is absent from pigs' livers, while adenase and xanthin oxidase are present. It is interesting that Mendel and Mitchell[2] have found in the liver of the embryo pig at an early age the same specific enzymes as characterize the liver of the adult animal. There was, however, a considerable delay in the appearance of the enzyme which oxidizes uric acid (see below). It is a curious phenomenon that pigs suffer from guanin gout. Oxyadenin has been discovered in pigs' blood.[3] Their normal urines contain not only uric acid,[4] but also large amounts of purin bases.[5] The organs of the pig are deficient in guanase.[6]

Schittenhelm[7] reports that human livers have the power to form uric acid from added purins, and he believes that the power to oxidize uric acid exists.

[1] Jones, W., and Austrian, C. R.: Z. physiol. Chem., 1906, **48**, 110.
[2] Mendel, L. B., and Mitchell, P. H.: Am. J. Physiol., 1907–08, **20**, 97.
[3] Buell, M. V., and Perkins, M. E.: J. Biol. Chem., 1927, **72**, 745.
[4] Schittenhelm, A., and Bendix, E.: Z. physiol. Chem., 1906, **48**, 140.
[5] Mendel, L. B., and Lyman, J. F.: J. Biol. Chem., 1910–11, **8**, 115.
[6] Jones, W., and Austrian, C. R.: Z. physiol. Chem., 1906, **48**, 110.
[7] Künzel, W., and Schittenhelm, A.: Zentralbl. gesam. Physiol. u. Path. d. Stoffw., 1908, **3**, 721.

Lauder Brunton[1] says that Stockvis, of Amsterdam, in 1860 found that crushed tissue had the power to destroy uric acid. This question has come into prominence and it has been shown that different organs have different powers in this regard, and that the same organ in animals of different species may behave quite differently.

Wiener[2] showed that dogs' liver and pigs' liver destroyed uric acid, whereas calves' liver had less power to do so, or none at all. The kidney pulp of various animals also destroyed uric acid.

Schittenhelm[3] finds that in cattle the spleen, lungs, liver, intestine, and kidney have the power of converting purin bases into uric acid in the presence of a constant oxygen supply. He finds a complete transformation of adenin, as follows: adenin, hypoxanthin, xanthin, uric acid. Guanin in like manner becomes xanthin and this again is converted into uric acid.

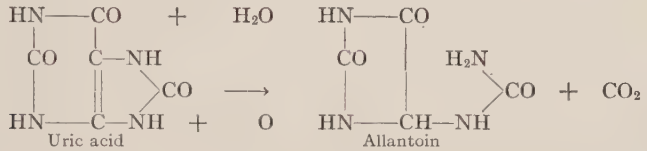
THE CHEMICAL PHYSIOLOGY OF THE PURINS

Minkowski[4] has shown that if a man ingest hypoxanthin the quantity of uric acid increases in his urine. He also showed that if a man ingest thymus gland, the nuclein of which yields principally adenin, the amount of uric acid is increased in the urine. If the thymus be given to a dog, the uric acid plus allantoin elimination is increased. Allantoin is an oxidation product of uric acid more frequently found in dogs' than in human urine. Minkowski discovered finally that adenin when administered to a dog did not increase the uric acid elimination, and was not excreted as such, but on autopsy of the dog the uriniferous tubules were found to contain crystals the chemical structure of which showed them to be aminodioxypurin. *In other words, adenin administered combined in nucleic acid loses its amino (NH_2) group, receives three atoms of oxygen, and is thereby converted into uric acid; adenin administered as such receives two atoms of oxygen, but does not lose its NH_2 group at the point for the attachment of the third atom of oxygen.* This work attests a varying behavior of purin bodies in accordance with their method of chemical union with other substances, and offers a suggestive key to certain relations observed in gout (p. 746).

[1] Brunton, Lauder: Centralbl. f. Physiol., 1905, **19**, 5.
[2] Wiener, H.: Arch. exp. Path. u. Pharm., 1899, **42**, 375.
[3] Schittenhelm, A.: Z. physiol. Chem., 1905, **45**, 145.
[4] Minkowski, O.: Arch. exp. Path. u. Pharm., 1898, **41**, 375.

When theophyllin, caffein, and theobromin, the methylated purins found in tea, coffee, and cocoa, are ingested it has been stated that they are not oxidized to uric acid, but that they increase the purin bases in the urine.[1] However, both Levinthal[2] and Stanley Benedict[3] have found the uric acid elimination to increase in man after the ingestion of 1 to 1.5 gram of caffein daily.

It is only recently that evidence has accumulated to show that the long believed physiologic oxidation of uric acid with the production of urea is impossible. To understand the subject it is necessary to consider the significance of allantoin which was first discovered by Wöhler in cows' urine in 1849. Salkowski[4] reported that the allantoin excretion increased in dogs after the administration of uric acid. The transformation of uric acid into allantoin takes place after the following reaction:



Uric acid Allantoin

Cohn[5] gave large amounts of thymus to a dog and found that the excretion of allantoin was greatly increased, though this did not happen in man, and experiments by Minkowski,[6] performed during the same year, showed that when hypoxanthin was fed to a dog 77 per cent. of it appeared in the urine as allantoin, while 4 per cent. was eliminated as uric acid. Mendel and White[7] found that allantoin was eliminated in the urine of cats and dogs after the intravenous administration of urates.

It was long believed that allantoin was an intermediary product of the oxidation of uric acid. It is due to Wiechowski that the subject has become clarified. Wiechowski[8] found that uric acid digested with the pulp of dogs' liver was oxidized completely to allantoin and no further, and also that uric acid injected subcutaneously into a dog

[1] Krüger, M., and Schmid, J.: Z. physiol. Chem., 1901, **32,** 104.
[2] Levinthal, W.: *Ibid.*, 1912, **77,** 259.
[3] Benedict, S. R.: "The Harvey Lectures," Philadelphia and London, 1915–16, p. 346.
[4] Salkowski, E.: Ber. d. d. chem. Ges., 1876, **9,** 719.
[5] Cohn, T.: Z. physiol. Chem., 1898, **25,** 507.
[6] Minkowski, O.: Arch. exp. Path. u. Pharm., 1898, **41,** 375.
[7] Mendel, L. B., and White, B.: Am. J. Physiol., 1904–05, **12,** 85.
[8] Wiechowski, W.: Hofmeister's Beitr. chem. Physiol. u. Path., 1907, **9,** 295; 1908, **11,** 109.

was almost completely eliminated as allantoin in the urine. These results were dependent upon the accurate method for the determination of allantoin which had been devised by the experimenter. It is evident, therefore, that the oxidizing enzyme uricase, which acts upon uric acid, carries its destructive power only as far as the production of allantoin, which is the end-product of purin oxidation.

An experiment[1] made many years ago demonstrated that if an Eck fistula, which excludes the portal blood from the liver, be created in a dog, uric acid appears in increased quantity in the urine. The interpretation long placed upon this was that in the absence of the liver uric acid was not oxidized. Repeating this experiment, Abderhalden, London, and Schittenhelm[2] found that the increase in uric acid elimination was compensated for by a decrease in allantoin excretion. The percentage values, contrasted with those in normal dogs' urine as established by Wiechowski, were as follows:

	Eck Fistula	Normal
Allantoin	74–87	94–97
Uric acid	12– 8	2– 4
Purin bases	1– 2	1– 2

Mann[3] and his coworkers state that the conversion of uric acid into allantoin depends on the presence of the liver, as the process ceases as soon as the liver is removed. Gremels and Bodo[4] find that uric acid added to the perfusate is eliminated by the isolated perfused kidney, whereas if a heart-lung-liver-kidney preparation is used allantoin appears in the urine, indicating that the oxidation of uric acid takes place in the liver and that the oxidation product is allantoin.

Wiechowski found that the allantoin excretion of the cat followed the same laws as obtain in the dog, and Hunter and Givens[5] report that the extent and behavior of the allantoin excretion of the Wyoming coyote is practically identical with that of the dog.

Hunter and Givens[6] state that the excretion of purin bases in the monkey greatly exceeds the elimination of uric acid, a condition

[1] Hahn, M., Massen, O., Nencki, M., and Pawlow, J.: Arch. exp. Path. u. Pharm., 1893, **32**, 191.
[2] Abderhalden, E., London, E. S., and Schittenhelm, A.: Z. physiol. Chem., 1909, **61**, 413.
[3] Bollman, J. L., Mann, F. C., and Magath, T. B.: Am. J. Physiol., 1925, **72**, 629.
[4] Gremels, H., and Bodo, R.: Proc. Roy. Soc. (London), 1926, B **100**, 336.
[5] Hunter, A., and Givens, M. H.: J. Biol. Chem., 1910–11, **8**, 449.
[6] Hunter, A., and Givens, M. H.: *Ibid.*, 1914, **17**, 37.

which also appears in the horse, sheep, pig, and goat. For the monkey the percentage figures are:

	Per Cent. Purin N
Uric acid	7–8
Allantoin	67
Purin bases	25–26

When allantoin was given subcutaneously to the monkey 75 to 90 per cent. was recovered in the urine.

Hunter and Givens[1] present the following table showing the relative purin content in the urines of various species of animals:

Order and Species	Per Cent. of Purin—Allantoin Nitrogen		
	Allantoin	Uric Acid	Bases
Marsupialia:			
Opossum	76.0	19.0	6.0
Rodentia:			
Guinea-pig	91.0	6.0	3.0
Rat	93.7	3.7	2.7
Ungulata:			
Sheep	64.0	16.0	20.0
Goat	81.0	7.0	12.0
Cow	92.1	7.3	0.7
Horse	88.0	12.0	0.5
Pig	92.3	1.8	5.8
Carnivora:			
Raccoon	92.6	5.4	2.0
Badger	96.9	1.9	1.2
Dog	97.1	1.9	1.3
Coyote	95.6	2.6	1.8
Primates:			
Monkey	66.0	8.0	26.0
Man	2.0	90.0	8.0

An extraordinary exception to the rule of oxidation of uric acid to allantoin in the dog was discovered by Stanley Benedict[2] to be characteristic of the Dalmatian hound, or spotted coach dog. The urines of these dogs contain large amounts of uric acid. When uric acid is administered subcutaneously it is completely eliminated in the urine instead of being oxidized to allantoin, as would happen ordinarily in the dog. This is a peculiar racial anomaly. Onslow[3] states that a cross between a Dalmatian and a normal dog, excretes uric

[1] Hunter, A., and Givens, M. H.: J. Biol. Chem., 1914, **18**, 403.
[2] Benedict, S. R.: "The Harvey Lectures," Philadelphia and London, 1915–16, p. 346. Confirmed by Wells, H. G.: J. Biol. Chem., 1918, **35**, 221.
[3] Onslow, H.: Biochem. J., 1923, **17**, 334.

acid to the amount given by a normal dog. Hence the power to oxidize uric acid is a dominant characteristic in the dog.

Loewi[1] showed that the ingestion of the same amount of nucleoprotein-containing food by different people resulted in the excretion of the same increased quantity of uric acid in the urine, and he surmised that the uric acid which was produced in the human being was not oxidized. Confirmation of this idea was given by the discovery of Soetbeer and Ibrahim[2] that the subcutaneous injection of uric acid in man led to its complete elimination in the urine.

For a long time this viewpoint was discredited by experiments which showed only a moderate recovery of uric acid in the urine when purin bases in measured quantities were given to human beings. These results, which were interpreted to be due to the oxidation of the purins through the uric acid stage, are now attributed to their non-absorption or their putrefaction in the intestinal tract. Thus the experiments of Rother[3] show that the purin ring is split by the bacteria of the large intestine. Steudel and Ellinghaus[4] say that the German war bread produced intestinal fermentation which destroyed the purins of the diet and gout virtually disappeared among the population during the Great War.

The urine of man is almost free from allantoin and the 10 to 15 milligrams which Wiechowski found therein may be accounted for as originating from traces of the substance found in common foods.[5]

Wiechowski[6] found that allantoin injected subcutaneously is completely eliminated in human urine, which is normally free from it. He also found that human tissues have no power to oxidize uric acid; it can always be completely recovered. Therefore the human organism lacks the enzyme uricase.

In concordance with these results Umber and Retzlaff[7] find that if uric acid be dissolved in piperazin and be injected into a healthy human being, between 80 and 95 per cent. may be recovered in the urine; also Levinthal[8] injected 1 gram of xanthin dissolved in piperazin into the vein of a healthy human subject, and concluded that,

[1] Loewi, O.: Arch. exp. Path. u. Pharm., 1900, **44,** 1.
[2] Soetbeer, F., and Ibrahim, J.: Z. physiol. Chem., 1902, **35,** 1.
[3] Rother, J.: *Ibid.*, 1921, **114,** 149.
[4] Steudel, H., and Ellinghaus, J.: *Ibid.*, 1923, **127,** 291.
[5] Ackroyd, H.: Biochem. J., 1911, **5,** 400.
[6] Wiechowski, W.: Arch. esp. Path. u. Pharm., 1909, **60,** 185.
[7] Umber, F., and Retzlaff, K.: Verhandl. d. 27ten Congresses für inn. Med., 1910, Sec. III, p. 436.
[8] Levinthal, W.: Z. physiol. Chem., 1912, **77,** 259.

in all probability, all the xanthin which reached the metabolic circulation was completely eliminated without the rupture of the purin nucleus, the larger part (82 per cent.) being oxidized to uric acid and only a small remainder (7 per cent.) passing unchanged through the organism.

The important experiments of Thannhauser and Bommes[1] deserve attention. When adenosin and guanosin were administered subcutaneously to normal men, between 75 and 82 per cent. of the purin bases contained in them were eliminated in the urine of the following twenty-four to forty-eight hours in the form of uric acid. These water-soluble purin-glucosids, adenosin and guanosin, are undoubtedly intermediary metabolites of nucleic acids.

A valuable *Habilitationschrift* by Severin was published from Minkowski's clinic at Breslau in 1916 and more briefly in abstract form later.[2] Severin partook for 3 weeks of a diet free from purins which contained per day 1.5 liters of milk, 75 gm. of butter, 150 gm. of bread, and 5 eggs. Continuing the diet, he added at different times individual purin-containing substances, each portion having a nitrogen content of 0.66 gm. (The nitrogen of the NH_2 group in adenin and guanin was not included.) The substance to be tested was administered either in 3 doses *per os* at 11, 12, and 1 o'clock or was given in 14 small doses every hour. Both methods of

THE ELIMINATION OF EXOGENOUS PURINS

Purin N in Diet = 0.66 Gm. (Exclusive of NH_2-N)	When Given Every Hour in 3 Doses. Per Cent. of Ingested Purin N Eliminated as				When Given Every Hour in 14 Doses. Per Cent. of Ingested Purin N Eliminated as			
	Uric Acid N	Purin N	Feces N	Total N	Uric Acid N	Purin N	Feces N	Total N
Raw thymus	31.8	....	5.3	....	35.6	....	6.5	
Hydrolyzed thymus	20.9	5.0	1.8	....	24.7	3.5	5.3	
Guanylic acid	....	....	....	....	58.3	....	3.9	
Guanosin	60.2	....	....	60.2	59.4	1.21	....	60.6
Adenosin	39.6	....	....	39.6	56.8	....	3.5	60.3
Xanthosin	47.9	2.1	....	50.0	50.3	....	....	....
Inosin	....	....	....	....	67.0	....	5.7	72.7
Guanin	....	....	....	....	33.8	3.2	10.8	
Adenin	29.7	11.5	....	....	27.1	12.7	4.1	
Xanthin	6.1	....	5.6	....	12.1	....	15.3	
Hypoxanthin	51.5	....	2.6	....	53.9	....	....	

[1] Thannhauser, S. J., and Bommes, A.: Z. physiol. Chem., 1914, **91**, 336; Thannhauser and Schaber, H.: *Ibid.*, 1921, **115**, 170.

[2] Severin, J.: Arch. exper. Path. u. Pharm., 1926, **115**, 205.

administration gave essentially the same results. Extra purin nitrogen appeared in the urine for 2 or 3 days. The source of the amount which appeared above the basal endogenous purin elimination was attributed to the elimination of exogenous purin. Severin's results are shown in the accompanying table.

A study of this table suggests the following facts: (1) that hypoxanthin is far more soluble than xanthin and is therefore much better absorbed; (2) that the oxidation of these two purins is a matter of absorption; (3) that adenin and guanin in organic combination are much more readily oxidized to uric acid than when they are in a free form; (4) that the oxypurins are much more readily oxidizable than the amino-purins, adenin and guanin; (5) that the liver ferments do not act readily on the last two free bases and, if absorbed, that they largely increase the purin base nitrogen in the urine.

This work of Severin coincides with what is known of the behavior of the purins. One may attribute the lack of complete recovery to intestinal putrefaction.

It should be here stated that *there are some who still believe that uric acid may itself be oxidized in the body.* Among these is Rother,[1] of Kraus's clinic in Berlin, whose denial of the validity of Thannhauser's work with guanosin and adenosin has been vigorously rejected by Thannhauser himself (see p. 737). Another notable believer that uric acid is partly destroyed in the body is Folin.[2] In a long paper this author and his associates report that uric acid injected into the blood stream of animals (dogs, cats, rabbits, and goats) is removed by the substance of the kidney so that this organ may contain as much as 0.2 per cent. Uric acid not so lodged remains in the blood and is there rapidly destroyed. The uric acid destruction stops the instant the blood is removed from the living animal. The oxidizing agent is therefore used up as soon as it is poured into the blood. The agency cannot therefore be an enzyme. The tissues appear to be impermeable to soluble urates. This Folin illustrates by stating that in birds the normal kidney contains 0.1 per cent. of uric acid, the blood 0.007 per cent., and the muscles 0.002 per cent. Intravenous injections of uric acid given as lithium urate to normal men are followed by the urinary excretion of between 30 and 90 per cent. of the material during 1 to 4 days after the injection. The authors confirm S. R. Bene-

[1] Rother, J.: Z. physiol. Chem., 1920, **110**, 245.
[2] Folin, O., Berglund, H., and Derick, C.: J. Biol. Chem., 1924, **60**, 361.

dict's work in finding in the Dalmatian hound a recovery of 80 per cent. of uric acid intravenously administered.

As pointed out above, many of the earlier experimenters obtained results contrary to those reported by Folin concerning destruction of uric acid in the human body. Delayed excretion of the admittedly difficultly excreted uric acid might be given as an explanation of Folin's results. Until a definite increase in allantoin excretion following uric acid ingestion by the human being has been shown, the conclusion that uric acid destruction occurs in man will remain open to question.

The Effect of Purins upon the Respiratory Metabolism.—Michael Ringer and Rapport[1] administered to dogs 20 gm. of nucleic acid in the forms of yeast and thymus nucleic acids dissolved in a soup made of Liebig's extract of beef and found that the metabolism of the dogs remained essentially at the level of the basal metabolism for a period of 6 hours after the administration of either of these substances. Hence nucleic acids and their decomposition products exert no specific dynamic effect. Phosphoric acid would not be expected to raise the metabolism, the carbohydrate content would be too small to do so, and the oxidative transformation of the purin bases into allantoin would be too trivial appreciably to modify the basal metabolism.

The synthetic origin of purins in metabolism has been recognized since the work of Miescher (see p. 80). Kossel[2] showed that purins developed in the incubated egg, which when newly laid is free from them (see also p. 511).

It has been made clear that in mammals the purins may be derived from ingested nucleoproteins, but this cannot be the only source, since purins are found in the urine during starvation and on a diet free from purins. This indicates a constant production of these substances in metabolism. Uric acid and purin bases from this source have been termed *endogenous* by Burian and Schur, in contradistinction to those which are eliminated after the ingestion of nuclein-containing food, which are called *exogenous*.

Burian and Schur[3] also established the fact that while the endogenous uric acid elimination varied between 0.3 and 0.6 gram daily, according to the individual, it did not vary in the same individual, but was a constant factor in his metabolism.

[1] Ringer, M., and Rapport, D.: J. Biol. Chem., 1923–24, **58**, 475.
[2] Kossel, A.: Z. physiol. Chem., 1886, **10**, 248.
[3] Burian, R., and Schur, H.: Pflüger's Arch. gesam. Physiol., 1901, **87**, 239.

A purin-free diet is obtained by giving such articles of food as milk, eggs, bread, potatoes, fats, and sugars, none of which contains nuclear material which forms exogenous purins in the body. Burian and Schur found that on such a diet the uric acid elimination was entirely independent of the quantity of protein ingested. It has been demonstrated by Rockwood[1] that the endogenous uric acid elimination is independent of the caloric value of the diet. Addition of 500 calories contained in maple sugar to a diet containing 2500 calories did not affect the excretion of uric acid. Rockwood's experiments extended over a long period of time. His individuals were nourished on milk, eggs, white bread, crackers, cheese, apples, and butter. The constancy of the uric acid output in the same individual is seen in the following table—in one case the record covering nearly a year:

TABLE SHOWING THE CONSTANCY OF THE DAILY ENDOGENOUS URIC ACID EXCRETION IN THE SAME INDIVIDUAL (TWO SUBJECTS)

Person A.	Date, 1903	Urine N in Grams	Uric Acid, Grams
	January	11.99	0.308
	February	11.58	0.305
	March	11.15	0.315
	May	12.63	0.321
	July	12.68	0.313
	November	9.99	0.298
Person B.			
	January	13.41	0.478
	March	13.92	0.452

This total shows the constancy of the output of endogenous uric acid in the same individual during a long period. Here the difference in the behavior of two individuals may be ascribed to a personal idiosyncrasy as regards the capacity for producing uric acid. From the record of Chittenden's[2] experiments, which covered a period of twenty-one months, it may be observed that a very low protein diet and moderate intake of food were without effect on the output of uric acid.

The source of the endogenous purins has been the cause of considerable speculation. In birds there is a large synthetic production of uric acid in the liver, for Minkowski[3] has shown that extirpation of the liver in geese leads to a replacement of uric acid by ammonia and lactic acid in the urine. The following analyses[4] give an idea of the composition of the urine of birds:

[1] Rockwood, E. W.: Am. J. Physiol., 1904–05, **12**, 38.
[2] Chittenden, R. H.: "Physiological Economy in Nutrition," New York, 1904, p. 24.
[3] Minkowski, O., and Naunyn, B.: Arch. exp. Path. u. Pharm., 1886, **21**, 41.
[4] Szalagyi, K., and Kriwuscha, A.: Biochem. Z., 1914, **66**, 126.

	Duck's Urine (Total N = 0.615 Gm.) Per Cent.	Fowl's Urine (Total N = 0.759 Gm.) Per Cent.
Ammonia	3.20	1.49
Urea	4.19	0.99
Uric acid	77.88	85.86
Purins	0.53	1.69
Colloidal N	4.09	
Amino-acid	2.71	2.52
Unknown	7.40	7.45
	100.00	100.00

The method of the synthetic production of purins is entirely conjectural.

Ingestion of pyrimidin bases (p. 725) has failed to yield purins in the organism.[1]

Burian[2] has investigated the source of the endogenous purins and comes to the conclusion that only a small part of the endogenous uric acid arises from the nucleoproteins of cellular tissue or those of dead leucocytes. It would require too large a destruction of tissue to provide from 0.3 to 0.6 gram uric acid or 0.1 to 0.2 gram purin nitrogen daily in the urine if it all arose from cell nuclein.

Burian and Schur's[3] analyses, showing the content of purin nitrogen in various tissues, are given below:

TABLE SHOWING THE QUANTITY OF PURIN N CONTAINED IN 100 GRAMS OF DIFFERENT ANIMAL TISSUES

	Total Purin N	N in Free Purin Bases
Meat	0.06	0.045
Thymus	0.45	0.05
Calves' liver	0.12	0.033
Calves' spleen	0.16	0.046

To obtain the amount of endogenous uric acid present in the urine, if it were produced by the destruction of nucleoproteins, it would be necessary to destroy completely a quantity of nucleoprotein equal to that contained in more than 100 grams of liver. It does not seem possible that nuclein destruction or nuclein metabolism could reach this extent.

Burian concludes that in the resting muscle there is a constant production of hypoxanthin which is converted into uric acid through the activity of the xanthin oxidase. In the active muscle there is a greater production of hypoxanthin which is not completely oxidized on account of a local oxygen deficiency.

[1] Steudel, H.: Z. physiol. Chem., 1903, **39**, 136.
[2] Burian, R.: *Ibid.*, 1904–05, **43**, 532.
[3] Burian, R., and Schur, H.: Pflüger's Arch. gesam. Physiol., 1900, **80**, 308.

It had been found by many previous observers that exercise has no effect on the purin excretion in the urine of twenty-four hours in man. Burian, however, finds a large increase in the purin elimination for an hour or two after severe muscular exercise, and this is followed by a compensatory reduction in the output during those subsequent hours which represent the interval of weariness in the muscle.

These observations were confirmed by the work of Rockwood,[1] who saw that the purin excretion was less during the night than during the day, and by the work of Pfeil,[2] who found a constant morning rise in the output of purins in human urine.

These facts confirm Burian's contention that the most general source of endogenous purins is a constant production of hypoxanthin in muscle, a production which varies with the individual and is possibly proportional to the mass of his musculature. Comparable to this is the constant production of creatinin (p. 253). Such of the purin bases as escape oxidation may be excreted by the blood flowing through the kidney even as uric acid is excreted under the same circumstances.

Sivén[3] does not believe that muscular work appreciably raises the production of endogenous purins. He thinks that the reduction in purin elimination during the night time is due to general inactivity of all the tissues, and shows that when an evening meal containing much protein is taken and the kidney is made thereby to functionate during the night, then the purin elimination is increased. Burian's discovery of increased elimination during work was perhaps due to the fact that the work was accomplished during the morning hours, when an increased elimination due to purins retained during the night would normally occur.

Steudel and Ellinghaus[4] report that when taking a purin-free diet a man excretes only 6 milligrams of purin bases per liter of urine. The purin bases of human urine are usually derived from tea and coffee.

Mendel and Brown[5] have determined the hourly excretion of uric acid as influenced by the ingestion of meat, liver, and other animal

[1] Rockwood, E. W.: *Loc. cit.*
[2] Pfeil, P.: Z. physiol. Chem., 1903–04, **40**, 1.
[3] Sivén, V. O.: Abstract in Zentralbl. gesamt. Physiol. u. Path. d. Stoffwech., 1906, **1**, 81.
[4] Steudel, H., and Ellinghaus, J.: Z. physiol. Chem., 1923, **127**, 291.
[5] Mendel, L. B., and Brown, E. W.: J. Am. Med. Assn., 1907, **49**, 896.

tissues. The increase in the eliminated uric acid is very marked and reaches a maximum two or three hours after the ingestion of these animal tissues. Thus after the ingestion of 600 grams of chopped meat the uric acid elimination, which had been 19 milligrams, rose during the following three hourly periods to 28, 88, and 98 milligrams, and then fell in successive hours to 79, 73, 51, 36, 25, and 22 milligrams. It will be seen later that such curves of exogenous uric acid excretion do not occur in the gouty patient in whom there is uric acid retention (see p. 748).

The studies of Stanley Benedict[1] concerning the uric acid content of the blood have brought to light some new and important facts. Fowl's blood had heretofore been accounted much richer in uric acid than ox blood. Benedict found this to be true only of the blood-serum, which in the fowl contains uric acid which circulates uncombined, whereas the blood-serum of the ox is almost entirely free from uric acid. Considered as a whole, however, ox blood yields 0.50 milligram of uncombined uric acid in 100 c.c. of blood. This is the amount which had been previously reported, but after hydrolysis 6.7 milligrams of uric acid were isolated and identified. This is entirely contained in the corpuscles and amounts to 50 per cent. more than the uric acid content of chickens' blood. These results throw additional light upon Minkowski's conception of the nature of gout, soon to be considered.

GOUT

The subject of gout is one of the most baffling in the literature of metabolism. Despite the brilliant work upon the purins during the last twenty years, work which has been illuminated by the discovery of the formula of nucleic acid by Levene, the nature of gout remains as much of a mystery as ever.

Just as the whole trouble in diabetes turns upon the inability of the organism to destroy sugar, so the symptoms manifested in gout are dependent upon the deposit of acid urate of sodium in certain localities. One of the earliest descriptions of gout comes from Sydenham, who suffered for forty years from the disease and published an extended account of it in 1683. It was Garrod[2] who first established the fact that uric acid was present in the blood of gouty

[1] Benedict, S. R.: J. Biol. Chem., 1915, **20**, 633.
[2] Garrod, A. B.: "The Nature and Treatment of Gout," London, 1859.

persons. He believed that this excess of urate was the cause of gout, the excess being deposited from the blood in the joints in the form of crystals. The problem of metabolism in gout is a problem of the factors entering into the cause of this deposit of urate. The general metabolism, exclusive of the purin factor, is exactly the same as in health. Magnus-Levy[1] proved that the oxygen absorption and carbon dioxid elimination is the same in gout as in health. The cause of the trouble must be sought elsewhere than in a reduced general oxidation power of the tissues.

Cecil, Barr, and DuBois[2] investigated four patients with acute and sub-acute arthritis, one patient with gout, and four with arthritis deformans and found the basal metabolism normal in all the patients except one who had a fever, and this patient regained his normal basal metabolism when his temperature returned to normal. To one of the patients suffering from arthritis deformans a maintenance diet containing between 2 and 3 gm. of nitrogen was given, and only 2.7 to 3.6 gm. of urinary nitrogen were found in the day's urine, indicating that there is no toxic destruction of protein in chronic arthritis. The disturbance is evidently limited to the purin metabolism.

Abelin and Blumberg[3] recorded the influence of fasting upon the uric acid output of a man with severe gout. They found that the high level of 0.4 to 0.5 gm. of urinary uric acid per day, when the man was taking a purin-free diet, was continued almost unchanged throughout the period of a fast of 5 days.

Clinical experience teaches that the predisposing causes are excessive eating, little muscular exercise, the abuse of alcoholic beverages, and lead-poisoning.

Beebe[4] has administered alcohol in various forms to a normal individual. He finds that even large doses have no effect on the hourly excretion of uric acid in a fasting man. The endogenous purin metabolism is therefore unchanged by the ingestion of alcohol. It is important to know that alcohol is apparently without effect upon such part of the purins as may be directly derived from cell metabolism. Further investigation of this subject by Landau[5] has revealed the fact that the influence of alcohol is different in different individ-

[1] Magnus-Levy, A.: Berliner klin. Wchnschr., 1896, **33**, 416.
[2] Cecil, R. L., Barr, D. P., and DuBois, E. F.: Arch. Int. Med., 1922, **29**, 583.
[3] Abelin, J., and Blumberg, M.: Biochem. Z., 1917, **81**, 1.
[4] Beebe, S. P.: Am. J. Physiol., 1904, **12**, 13.
[5] Landau, A.: Deut. Arch. klin. Med., 1909, **95**, 280.

uals, and that usually there is a slight increase in the output of endogenous purins after taking alcohol. Mendel and Hilditch[1] report the same results. Administration of alcohol equal to 500 calories, together with a purin-free diet, to a man previously unaccustomed to alcohol caused a slight decrease in the elimination of nitrogen and a slight increase in that of uric acid. Otherwise the urinary analysis showed little or no change, even when alcohol was administered for weeks.

Pollak[2] has shown that in chronic alcoholics the retention of ingested purins is favored.

Steudel and Ellinghaus[3] attributed the disappearance of gout among the German people to the ingestion of war bread, which induced active intestinal putrefaction and thereby destroyed the purin precursors which are the sources of exogenous urinary purins (see p. 736). These authors say that one may speak of "alimentary arthritis" due to favorable conditions for the absorption of nucleotids and nucleosids from the intestinal tract. They state that at Karlsbad only few nuclein bases are absorbed, that solvents for uric acid are not required for treatment, but on the contrary the prevention of the absorption of purin-containing materials is the important factor. For in the gouty patient the intestinal absorption of purins may precipitate an attack of gout.

Severin, whose work has just been described, has defined the views of Minkowski upon the theory of gout. In 1903 Minkowski thought that uric acid occurred in the blood in combination with nucleic acid, thus creating a compound which determined the solution, transport, and destiny of uric acid in the body. After the discovery of the formula of nucleic acid by Levene, and the synthetic production by Emil Fischer[4] of a very soluble, easily dissociable d-glucosid of trimethyl-uric acid, Minkowski reformulated his old hypothesis in the light of the probable existence of an organic compound of uric acid in the form of a labile, easily dissociable, very soluble nucleotid or nucleosid. Normally the kidney loosens this uric acid from its combination and removes it. In gout the kidney does not do this, hence uric acid rises in the blood and the cleavage of this compound takes place in the cartilage with the deposition of urates.

[1] Mendel, L. B., and Hilditch, W. W.: Am. J. Physiol., 1910–11, **27**, 1.
[2] Pollak, L.: Deut. Arch. klin. Med., 1906, **88**, 224.
[3] Steudel, H., and Ellinghaus, J.: Z. physiol. Chem., 1923, **127**, 291.
[4] Fischer, E., and Helferich, B.: Ber. deut. chem. Gesel., 1914, **47**, 210.

Amplifying an earlier conception of Minkowski, Severin postulates that perhaps the liver enzymes do not deaminize the purins of adenosin and guanosin in the normal fashion and that uric acid may be liberated in a form that may be specifically deposited in the gouty areas. Hence uric acid continually rises in the blood, which the affected kidneys cannot eliminate. In contrast with the gouty individual, the patient with leucemia compensates for a high uric acid content of the blood, induced by an increased purin metabolism, by an increased uric acid elimination, because such a person has an undisturbed purin ferment metabolism. In other words, the leucemic patient has a normal physiological nuclein metabolism which leads to the production of an easily soluble organically combined uric acid which is readily split in the kidney and therefore almost never creates deposits of urates in the tissues.

The opinions of other modern workers vary somewhat from those of Minkowski, as appears in the following:

Almagia,[1] in Hofmeister's laboratory, performed some very interesting experiments and concludes that the older view of Garrod is correct—that is, that an excess of urates in the blood is the cause of gout. Almagia found that thin strips of cartilage suspended in dilute neutral solutions of sodium urate absorbed the salt, did not destroy it, but caused it to be deposited in fine crystals within the cartilage. He furthermore injected 5 to 7 grams of uric acid into the peritoneal cavity of rabbits, a dose which usually killed them. On testing the liver, spleen, muscles, and lungs with the murexid test for uric acid, negative results were obtained, whereas cartilage gave a positive reaction indicating the presence of urates. Almagia concludes that the deposit of urates in the cartilage of a gouty patient is but the result of a temporary or permanent increase in the uric acid content of the blood. The liability of cartilage to contain deposits of urates has received no satisfactory explanation. Exposure to cold, stagnation of the blood flow, and the richness of cartilage in sodium salts have been suggested as possible reasons for the precipitation of the urates.

Folin, whose views upon normal purin metabolism have already been given (see p. 738), states that in gout the uric acid metabolism is essentially the same as in the normal person, but a characteristic lack of responsiveness of the kidney is exaggerated in gout, and this

[1] Almagia, M.: Hofmeister's Beitr. chem. Physiol. u. Path., 1906, **7**, 466.

is the reason why the gouty carry abnormally high levels of circulating uric acid. He remarks upon the possibility that cartilage and connective tissue like dead animal tissues, though unlike living muscle, may permit the slow passage of urates into the localities where urates are found in the gouty. Folin states that intravenous injections of 20 mg. of uric acid per kilogram of body weight do not produce attacks in the gouty, but may produce temporary injury to the kidney so that a rise of non-protein nitrogen and of urea takes place in the blood. In normal persons there is no such reaction. This is a beautiful demonstration of the abnormality of the kidney in gout.

In leucemia, where there must be a large destruction of nucleoprotein, as evidenced by a report concerning a patient who eliminated 12 grams of uric acid during the last forty hours of life, there is no gout.[1] Folin reports that normal human blood contains about 1.5 to 2.5 milligrams of uric acid per 100 c.c. and that this quantity is exceeded not only in gout but also in leucemia, lead-poisoning, and in nephritis. Folin and Denis[2] state that in true gout there is no increase in the quantity of non-protein nitrogen in the blood, though this increase appears in arthritis deformans. They recommend this as a means of differential diagnosis between gout and arthritis.

Magnus-Levy,[3] Vogt,[4] and Reach[5] were the first to discover that the administration of glands rich in nucleoprotein, such as thymus and pancreas, to gouty persons did not cause as large an excretion of uric acid in the urine as when the same amounts of these materials were given to normal individuals.

The work of Soetbeer[6] is of the best modern character, and illustrates the retention of uric acid in gout. Soetbeer compared the excretion of uric acid by gouty people during three-hour intervals with that of normal individuals, as observed by Pfeil (p. 742). In one case of long-standing gout, of light character and with long intervals between the attacks, there was little variation from the normal in the uric acid excretion. In another case of gout, a patient who was examined between the attacks showed no increase in uric acid output

[1] Magnus-Levy, A.: Virchow's Arch. path. Anat., 1898, **152**, 107.
[2] Folin, O., and Denis, W.: Arch. Int. Med., 1915, **16**, 33.
[3] Magnus-Levy, A.: Z. klin. Med., 1899, **36**, 414.
[4] Vogt, H.: Deut. Arch. klin. Med., 1901, **71**, 21.
[5] Reach, F.: Münchener med. Wchnschr., 1902, **49**, 1215.
[6] Soetbeer, F.: Z. physiol. Chem., 1903–04, **40**, 54.

after changing from a purin-free diet to one containing 320 grams of meat, and showed only a slight increase in elimination after 640 grams of meat were given. These results were obtained six weeks after the last attack and at a time when the patient was entirely free from pain. In still another case 350 grams of meat were given during the attack to a gouty patient who had no fever and whose urine was free from albumin and sugar. The results were as follows:

	Uric Acid in Grams
Diet free from purins	0.276
" " " "	0.328
Diet + 350 grams meat	0.316
" " " "	0.270
" " " "	0.255

In this experiment even during the days of purin-free diet there was no "morning rise" noted as a normal incident by Pfeil. The hourly uric acid excretion was very even. The kidney was apparently removing uric acid up to the limit of its capacity.

Hefter[1] administered uric acid subcutaneously to a gouty patient and recovered only 11 per cent. of it in the urine in contrast with a recovery of 86 per cent. in the normal individual. Thannhauser and Bommes[2] report that although between 75 and 82 per cent. of the purin content of 1 gram of adenosin when subcutaneously administered to normal men appears as uric acid in the urine, and the uric acid content of the blood does not rise, yet in severe gout this procedure is not followed by additional excretion of uric acid, though uric acid does increase in the blood. Three of four gouty patients had attacks of gout after this treatment. The authors state that the conclusion is unavoidable, that gout is due to a disturbance in the elimination of uric acid.

Thannhauser[3] finds no indication that any disease is caused by a pathological metabolism of nuclein. In differentiating between *primary constitutional gout* and *secondary gout* he states that the first is caused by a constitutional weakness of the kidney for the elimination of urates. On this account urates accumulate in the blood and cause a gradually developing acute nephritis. Secondary gout develops as the result of diffuse chronic kidney disease in which the urate eliminating power of the organ is diminished.

[1] Hefter, J.: Deut. Arch. klin. Med., 1913, **109,** 322.
[2] Thannhauser, S. J., and Bommes, A.: Z. physiol. Chem., 1914, **91,** 336.
[3] Thannhauser, S. J., and Czoniczer, G.: Deut. Arch. klin. Med., 1921, **135,** 224.

Denis[1] finds that there is no increase in the uric acid content of the blood of man after the ingestion of foods rich in purins, except in cases of renal insufficiency.

The drugs which are used in rheumatism, arthritis, and gout, such as salicylate of soda, aspirin, and atophan, cause an increased elimination of uric acid in the urine and a concomitant fall in the quantity of uric acid present in the blood.[2] Starkenstein[3] reports that when atophan is given to healthy men taking a diet free from purins, the uric acid output decreases the first day, increases the second to fourth days and then becomes normal and constant in output after daily doses of the drug. Salicylate of sodium when given in amounts to produce no salicylate intoxication (such as ringing in the ears) has no effect upon the basal metabolism of normal men though the uric acid and total nitrogen elimination is somewhat increased.[4]

The discovery of Stanley Benedict of the large amount of uric acid combined in the corpuscles of ox blood lends added significance to the idea of Minkowski that the deposition of urates in gout may be dependent upon some abnormal chemical union of the uric acid which breaks up, yielding urates for the construction of tophi. The possible importance of this factor should not be lost sight of.[5]

Miller and Jones[6] were unable to find any variation from the normal in the distribution of the purin enzymes in the tissues of a gouty individual.

Linser[7] tells how a gouty individual suffering from eczema was treated with the Röntgen rays. Although the person was on a purin-free diet, the treatment invariably brought on an attack of gout on account of the increased production of uric acid within the body which normally follows such treatment.

Gudzent[8] states that monosodium urate occurs in the blood in two isomeric forms, the more soluble *lactam* form being readily convertible into the less soluble and more stable *lactim* form, these having

[1] Denis, W.: J. Biol. Chem., 1915, **23,** 147.
[2] Jackson, H. C., and Blackfan, K. D.: Albany Med. Annals, 1907, **18,** 24; Rockwood, E. W.: Am. J. Physiol., 1909–10, **25,** 34; Fine, M. S., and Chace, A. F.: J. Biol. Chem., 1915, **21,** 371; Denis, W.: J. Pharm. and ex. Ther., 1915, **7,** 601.
[3] Starkenstein, E.: Biochem. Z. 1920, **106,** 139.
[4] Denis, W., and Means, J. H.: J. Pharm. and ex. Ther., 1916, **8,** 273.
[5] Minkowski, O.: Z. physiol. Chem., 1913, **88,** 159.
[6] Miller, J. R., and Jones, W.: *Ibid.*, 1909, **61,** 395.
[7] Linser, P.: Therapie der Gegenwart, 1908, **49,** 159.
[8] Gudzent, F.: Z. physiol. Chem., 1909, **63,** 455.

been chemically differentiated by Emil Fischer. While 100 c.c. of blood dissolve 18.4 milligrams of the first salt, they dissolve only 8.4 milligrams of the second. Gudzent[1] maintains that the inhalation of radioactive emanations leads to an increased elimination of uric acid in the gouty, due to the conversion of the lactim form of uric acid into the lactam form. However, Wiechowski[2] denies the influence of radium upon the solubility of uric acid, though he finds that the emanations bring about a rise in the elimination of uric acid not only in gouty persons but also in normal individuals. The emanations undoubtedly increase cell destruction, nuclear disintegration, and therefore an increase in the output of uric acid. There is little or no influence exerted by radium emanations upon the respiratory metabolism,[3] although it is stated that the ingestion of one hundred times the usual therapeutic dose has caused an increase in metabolism of 17 per cent.[4]

Von Noorden and Schliep[5] suggested that gouty patients be tested for their "tolerance" for purin bodies just as diabetics are tested for their tolerance for carbohydrates; 400 grams of meat contain 0.24 gram of purin nitrogen, which is the equivalent of 0.72 gram uric acid. A patient was put on a purin-free diet; was given 400 grams of meat, then put on a purin-free diet again, and afterward was tested with 200 grams of meat. The results were as follows:

Day	Diet	Uric Acid in Grams
4	Purin free	0.462
5	" " + 400 gm. meat	0.522
6	" " + 400 gm. meat	0.544
7	" "	0.539
8	" "	0.528
9	" "	0.458
10	" " + 200 gm. meat	0.549
11	" " + 200 gm. meat	0.655
12	" "	0.647
13	" "	0.499
14	" "	0.433

The authors concluded that while the increased uric acid output after giving 400 grams of meat was not what it would have been normally, yet after giving 200 grams the quantity of additional uric acid was fully eliminated. Hence this patient had a tolerance for the purins in 200 grams of meat.

[1] Gudzent, F.: Z. klin. Med., 1910, **71**, 304; 1913, **78**, 266.
[2] v. Knaffl-Lenz, E., and Wiechowski, W.: Z. physiol. Chem., 1912, **77**, 303.
[3] Silbergleit, H.: Berliner klin. Wchnschr., 1908, **45**, 13; 1909, **46**, 1205.
[4] von Benczúr, J., and Fuchs, D.: Z. exp. Path. u. Therap., 1912–13, **12**, 564.
[5] von Noorden, C., and Schliep, L.: Berliner klin. Wchnschr., 1905, **42**, 1297.

Dietetic rules for gouty sufferers are intended to combat the fundamental anomalies of the metabolism. The organism must not be overloaded with uric acid. Minkowski's rules[1] for treatment of gout may be thus abstracted: Sweetbreads, liver, and kidney are to be strictly excluded from the diet since they contain purin bases in large quantity. Meat is to be taken in moderation only. Wine should be taken sparingly or not at all, and beer rigidly excluded on account of the nuclein in yeast. Cathartics may be given to rid the intestine of purin bodies excreted into the intestinal canal, and water-drinking, which promotes a larger flow of urine and increased uric acid elimination, is strongly to be commended. The diet for a gouty patient should contain each day 100 or 120 grams of protein, 80 or 100 grams of fat, and 250 or 300 grams of carbohydrates (2200 to 2600 calories). This should not include more than from 200 to 250 grams of meat per day. Indigestible cakes, pies, rich foods, and heavy salads should be forbidden. Moderation and self-control are the watchwords for the gouty sufferer.

It is impossible to oxidize uric acid, and no treatment now known increases its solubility. Minkowski hopes that some organic compound may be discovered which will accomplish this purpose.

Great men have given earnest attention to the baffling problem of gout and arthritis and yet when all is considered there has been only moderate advance toward the understanding of these diseases during the past quarter century or since the following words were written for the first edition (1906) of this book: "Bearing the facts of the above discussion in mind, the reader will comprehend that present-day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries."

[1] Minkowski, O.: Deut. med. Wchnschr., 1905, 31, 409.

CHAPTER XXX

THE INFLUENCE OF CERTAIN DRUGS UPON METABOLISM

He that may be cured by diet must not meddle with physick.—ARNOLDUS.

IMPORTANT work concerning the influence of certain drugs upon the basal metabolism in normal men has been carried out by Higgins and Means[1] in Edsall's clinic at Boston. They present a summary of their findings in the following table:

THE INFLUENCE OF DRUGS ON METABOLISM

DRUG	AVERAGE DOSE	ACTION				
		RESPIRATORY CENTER	BRONCHIAL MUSCULATURE	METABOLISM	RESPIRATION RATE	PULSE-RATE
Atropin.....	1.0 mg.	None.	Dilation.	Increase.	None.	Fall, then rise.
Caffein.....	0.4 gm.	Stimulation.	Either dilation or none.	Increase.	Increase.	None.
Camphor.....	0.1 gm.	None.	Either dilation or none.	Generally slightly increased.	None.	None.
Strychnin.....	4.5 mg.	None.	Probably none.	None.	None.	None.
Morphin.....	16.0 mg.	Either depression or none.	Constriction.*	Either slight decrease or none.	Slight increase.†	None or decrease.
Heroin.....	5.0 mg.	Depression.	Constriction.	None.	None.	Slight decrease.

* Or none, when the bronchi are already constricted.
† This obviously does not apply to large doses of morphin.

They report that caffein caused a rise in the metabolism equal to 15 per cent. without changing the pulse-rate. The increase after camphor was 8 per cent. and after atropin only 4 per cent. above the normal basal metabolism. That therapeutic doses of strychnin cause no increase in metabolism is significant.

Interesting results of Means, Aub, and DuBois[2] show that large doses of caffein given to normal individuals cause an increase in the basal metabolism of 7 to 23 per cent. without increasing the pulse-rate or the body temperature.

[1] Higgins, H. L., and Means, J. H.: J. Pharm. and Exp. Therap., 1915, **7**, 1.
[2] Means, J. H., Aub, J. C., and DuBois, E. F.: Arch. Int. Med., 1917, **19**, 832.

The influence of large doses of caffein appears at first thought to be remarkable, the basal heat production rising to the level found after the ingestion of large quantities of meat. The increase is slight, however, when compared with the stimulation of metabolism by muscular exercise. It appears great only when compared with the immutability of the level of the normal basal metabolism, a state in which the heat production is subservient to the requirement of energy on the part of the cells for the maintenance of life, the requirement being so regulated and adjusted that the heat loss per square meter of surface is approximately 40 calories per hour, while the body temperature is maintained at a constant level.

Chanutin and Lusk[1] showed that morphin, given to a dog which went to sleep, caused an average fall of 6 per cent. during the 2d, 3d, and 4th hours, though the average fall during the 2d hour was 11 per cent., or the lowest found. The rectal temperature gradually fell between 1° and 2° C. after taking morphin. In one experiment it was calculated from the fall in rectal temperature that 18.1 calories were lost from the dog's body in 3 hours. Indirect calorimetry indicated that the heat production of the dog was 47.9 calories during the period. Direct calorimetry measured 66.0 calories given off by the dog by radiation and conduction and vaporization of water. The difference is 18.1 calories, or that lost from the dog's body on account of the fall in body temperature. The computations agree. Thirty-six per cent. more calories were lost from the body than were produced. More heat was lost by radiation and conduction alone (106 per cent.) than was produced. The metabolism was maintained nearly at the normal level despite a considerable fall in body temperature. When morphin was given to another dog it became hypersensitive and the basal metabolism rose 10 per cent.

McKeen Cattell[2] has noticed a slight fall in the metabolism of cats after administering morphin.

Aub, Bright, and Uridil[3] found that cats suffered no change in metabolism after taking urethan.

Deuel, Chambers, and Milhorat[4] investigated the influence of amytal upon the metabolism of dogs. They found that the basal metabolism was slightly lowered when 50 mg. per kilogram of body

[1] Chanutin, A., and Lusk, G.: J. Pharm. and Exper. Therap., 1922, **19**, 359.
[2] Cattell, McK.: Arch. Surg., 1923, **7**, 96.
[3] Aub, J. C., Bright, E. M., and Uridil, J.: Am. J. Physiol., 1922, **61**, 300.
[4] Deuel, H. J., Jr., Chambers, W. H., and Milhorat, A. T.: J. Biol. Chem., 1926, **69**, 249.

weight were given. Maximal doses cause a profound fall, as great as 35 per cent. being observed, which might or might not be compensated for by shivering. A typical experiment is presented below:

Type	Basal Metabolism		Hours after 65 Mg. Amytal per Kg.				
			2	3	4	5	6
R. Q.	0.81	0.79	0.84	0.86	0.86	0.92	0.89
Calories, indirect	27.3	27.6	26.3	27.1	27.1	26.0	26.7
Calories, direct	.....	.....	25.5	25.5	23.5	27.9	26.5
Rectal temperature, end of hour	39.2	38.8	36.9	36.7	36.3	36.3	36.1

The fall in body temperature scarcely affected the level of metabolism. It will be recalled that amytal is a drug which is without influence upon the level of the blood sugar (see p. 653).

Hines, Boyd, and Leese[1] find that the increase in the respiratory quotient and in the height of metabolism after intravenous injection of large amounts of glucose is just as great under amytal anesthesia as in the normal dog. The period of sugar injection by the Woodyatt pump method lasted 4 hours, and the blood sugar rose to between 0.400 and 0.470 per cent. (see p. 339). The average results upon 5 animals are given in the table below:

Period	R. Q.	Heat per Sq. M. per Hr.	Without Anesthetic	
			R. Q.	Cals. per Sq. M.
Preliminary	0.79	40.4	0.82	44.7
Glucose injection	1.00	63.4	0.98	67.9
Post injection, 1st hr	0.89	48.0	0.94	47.4
2d hr	0.93	41.5	0.88	49.8

The metabolism under amytal anesthesia appears to be only slightly divergent from the normal.

[1] Hines, H. M., Boyd, J. D., and Leese, C. E.: Am. J. Physiol., 1926, **76**, 293.

CHAPTER XXXI

FOOD ECONOMICS

Never shall I forget the kindness which the German student met at the hands of Arago, Dulong, and Thénard; and how many of my German countrymen, medical men, physicists, and orientalists could I name who like myself remember with gratitude the active support of their scientific aims which was liberally accorded them by French *savants*. Warm sympathy for all that is noble and great and disinterested hospitality are among the finest features of French character.—JUSTUS V. LIEBIG in 1871.

FOOD economics does not consist in the art of finding the cheapest food available. Matters of taste are extraordinarily varied. One recalls the oft quoted definition which Samuel Johnson put in his dictionary: "Oats.—A grain which is generally given to horses, but which in Scotland supports a people." And the quick response, "Where, Sir, do you find such horses as in England or such men as in Scotland?" A Frenchman would rather die than eat oatmeal. A German to whom it was offered in America said "No, I am a German." An American will eat corn bread, and during the war several of our southern states passed laws forbidding the use of wheat. But the British will not eat corn bread, both because they cannot cook it properly and because maize is indelibly stamped upon their imaginations as being fit only for pigs. The starving children of Belgium would not eat rice offered to them by Mr. Hoover. On the contrary, the Italian is happy only when he is surfeited with rice or macaroni. The European is astounded at the twenty-five or more courses of *hors d'oeuvres* of the Chinese dinner.

In spite of the fact that all races of men have presumably the same nutritive requirement in terms of energy, yet the fundamentals of nutritional psychology may be entirely different. Is it a wonder that the nations rage over misunderstandings often more theatrical than real?

THE GERMAN FOOD SITUATION IN THE WAR

The consideration of the food supply from a national standpoint was forced upon Germany at the outbreak of the great war. Eminent scientists combined in a report upon the prospects of the sustenance of the nation. Imports from oversea had been restricted. Meat,

butter, cheese, and fish formerly obtained from Holland and Denmark were no longer available. The North Sea fisheries which had yielded 179,000 metric tons (1 metric ton = 2200 lbs.) of fish were closed, trained farm hands were fewer, crops in East Prussia and Alsace had been destroyed, the situation appeared serious. It was estimated that the annual amount of food fuel necessary to support 68,000,000 Germans—men, women, and children—was 56,750,000,000,000 calories. This is the equivalent of 3000 calories per adult per day. The quantity of protein required in this fuel, if the human machines were to maintain themselves in self-repair, was estimated to be 1,605,000 metric tons per annum. It was calculated that a mixed population of 68,000,000 men, women, and children required the same amount of food as would 51,823,000 adults.

In order to increase the production of food and to diminish the waste the committee recommended increasing the crop of beans, with its large protein content, reducing the unnecessarily large meat supply, and increasing the intake of cheese and skimmed milk, which latter should no longer be fed to pigs, improving the yield of vegetables and fruits, and reducing the quantity of butter and cream produced.

A reduction in the consumption of meat, butter, and cream was necessary because edible grains would be required for human food, and the maintenance of the usual number of cattle was no longer deemed possible.

The estimated savings as above enumerated would result in a total production of 81.25 billion food calories containing 2,022,800 tons of protein.

The conditions were thus summarized:

TABLE SHOWING THE ANNUAL FOOD REQUIREMENTS OF 68,000,000 PEOPLE IN GERMANY

	Protein in 1000 Metric Tons	Calories in Thousand Millions
Actual requirement	1605	56.75
Used before the war	2307	90.42
Available (unchanged habits)	1543	67.86
Available (under present recommendations)	2023	81.25

From these data it was concluded that the German people, through coöperation of millions of inhabitants, would be able to prevent suffering for lack of food.

The writer is informed upon good authority that the food produced during 1914–16 never attained the level of production in peace times, that the food requirement of the population was underestimated for the physical work to be accomplished and underestimated for those who were in the period of adolescence; furthermore, that the enforcement of the food laws was placed in the hands of farmers, middlemen, and politicians, who mismanaged the situation.

THE INTERALLIED SCIENTIFIC FOOD COMMISSION

Lusk[1] has written elsewhere a brief description of the food situation of the allied countries during the difficult winter and spring of 1917 to 1918.

The Interallied Scientific Food Commission, which met in Paris late in March, 1918, adopted the following resolution: "That the requirements of the average man of 70 kilogram body weight doing 8 hours average physical work in a climate such as England's or France's is to be considered as 3300 calories *as purchased*."

It was decided that 3000 available calories *as ingested* were the requirement of the *average man*, leaving a 10 per cent. margin for domestic spoilage or waste.

The older standards of food for children had been found to be much too low. Thus, DuBois had just discovered that the basal metabolism of boys of 14 was as great in calories per day as that of their fathers, and it was believed that the same relation existed between girls of 14 and their mothers. This last fact was later demonstrated by Benedict and Hendry,[2] who found that the average basal metabolism of girls between 12 and 17 years of age varied only slightly from 1250 calories per day, in spite of an increase in weight.

A new set of standards was prepared by Lusk at the Paris meeting, which were as follows:

Age in Years	Coefficients	Utilizable Calories
0–6 (both sexes)	0.50	1500
6–10 (both sexes)	0.70	2100
10–14 (both sexes)	0.83	2500
14+ (males)	1.00	3000
14+ (females)	0.83	2500

[1] Lusk, G.: in "Essays and Studies in Honor of Margaret Barclay Wilson," New York, 1922, p. 64; also in "America and the New Era," by E. Friedman, New York, 1920, p. 369.

[2] Benedict, F. G., and Hendry, M. F.: Boston Med. and Surg. J., 1921, 184, 217 *et seq.*

Miss Dalyell has informed me that she and Miss Chick, when they worked in Vienna after the war, used these coefficients with success in determining whether a family was properly nourished or not.

Using these figures, it was possible to calculate the food requirements of a nation. That of the United Kingdom is shown in the following table:

ESTIMATE OF THE CALORIC REQUIREMENTS PER DIEM OF THE POPULATION OF THE UNITED KINGDOM IN 1911

Age in Years	Number	Calories per Person	Man Value	Calories in 1000 Millions per Diem	Per Cent.
0– 5	5,772,000	1,500	0.50	8,660	8
6– 9	3,709,000	2,100	0.70	7,790	7
10–13	3,548,000	2,500	0.83	8,870	8
14+ (males)	15,437,000	3,000	1.00	46,311	40
14+ (females)	16,808,000	2,500	0.83	42,020	37
	45,274,000	2,510	0.836	113,651	100

The national food requirement of the United Kingdom for a year reached 41.5 million million calories. Adding 10 per cent. for waste, the total became 45.6 million million calories. Now before this figure was arrived at the Royal Society of London had made the following estimate of the average annual food supply of the United Kingdom:

Home production	16.93	million	million	calories
Imported food	30.22	"	"	"
Total food	47.15	"	"	"

The equivalent of this supply of food "per man per day" is 3410 calories. This is a check on the value of 3300 calories per man per day and indicates that it is true to the needs of this great population.

For the year 1918–19 the following food requirements were estimated:

	Calories in Millions		
	United Kingdom	France	Italy
Total requirement	49,600,000	40,916,865	38,000,000
Home production	17,200,000	24,519,652	23,000,000
To be imported	32,400,000	16,397,213	15,000,000

The necessary imports of the United Kingdom alone were estimated as follows:

Imports, 1918–19	Metric Tons	Calories in Millions
Meat	1,140,000	3,667,000
Margarine	505,000	4,000,000
Sugar	1,300,000	5,330,000
Wheat	5,330,000	19,403,000
Total	8,275,000	32,400,000

The program as laid down became Hoover's export program for 1918–19. Think of the shipping necessary to transport upward of 8,000,000 metric tons of food to Britain annually. The yearly food bill is £500,000,000 sterling or two and a half billion dollars. This must be paid for in goods or services.

The thoughtful should realize that the conditions of existence in the heart of England, a food importing country, are entirely different from those in the heart of France, normally a self-providing country, or in the heart of the United States, a food exporting country. The necessary maintenance of her trade interests by the United Kingdom is the cause of much ignorant misunderstanding by minor politicians the world over.

We may pass now to the study of a small community, a boys' school.

FOOD INTAKE IN A BOYS' SCHOOL

F. C. Gephart,[1] of the Russell Sage Institute of Pathology, has made a study into the food consumption of the boys at St. Paul's School at Concord, New Hampshire, one of the largest private boarding-schools in the country. The total annual food supply may be thus computed:

SUPPLIES FOR BOYS' BOARDING SCHOOL

	Protein, Metric Tons	Fat, Metric Tons	Carbohydrate, Metric Tons
Food supply	20.5	25.6	60.5
Waste	3.8	5.4	4.2
Food-fuel	16.7	20.2	56.3

[1] Gephart, F. C.: Boston Med. and Surg. J., 1917, **176**, 17.

This quantity of nourishment was taken by 355 boys and also about 100 adults (masters and servants). When computed on the basis of the individual meals served it was divided as follows:

	Food Supply per Meal			
	Pounds	Grams	Calories	Calories Per Cent.
Protein	0.1107	50.2	206	14*
Fat	0.1332	60.4	562	39
Carbohydrates	0.3717	168.8	692	47
			1460	100

* 70 per cent. of this is in animal protein.

The pre-war cost of this food per meal was 20 cents, or 13.8 cents per 1000 calories. The food, which was bought by a purchasing agent in the Boston market, was of the best quality, and included 193 separate varieties.

These growing, athletic boys, however, were not satisfied with 3000 calories daily. They not only took 4350 calories daily at the table, but they bought 650 additional calories in food at a neighboring store, the principal item being chocolate.

Data concerning the subjects of the investigation are epitomized in the two following tables:

TABLE SHOWING THE NUTRITION CONDITIONS AT A SCHOOL CONTAINING 355 BOYS

	Average Age	Height	Weight	Body Surface	Basal Metabolism (Calc.)	Food	Food in Per Cent of Basal
	Years	Cm.	Kg.	Sq. M.	Cals.	Cals.	
The Upper School	16	172.7	60.6	1.73	1826	4997	274
The School	14½	165.1	50.8	1.54	1737	5126	295
The Lower School	13½	157.5	43.8	1.40	1647	4949	300

The basal requirement of boys is, as DuBois (see p. 139) has shown, 25 per cent. above that of the adult. The total fuel intake was three times that of this basal level which is the heat production when a boy is resting or asleep. The 5000 calories contained in the ingesta is half as much again as a farmer at work would require. The quantity of the calculated intake would certainly not be lowered by

excluding the adults who unavoidably entered into this computation. These data explain the ravenous appetite of boys. Lack of appreciation of this factor or lack of provision for it are the probable causes of much of the undernutrition seen in children of school age.

The distribution of the fuel values among the various more common articles taken as food at the school is shown in the following table:

PERCENTAGE DISTRIBUTION OF THE CALORIES INGESTED AT A BOYS' BOARDING SCHOOL

	Per Cent.		Per Cent.
Bacon	1.8	Lamb	5.3
Beef	6.7	Milk	12.6
Bread and flour	13.3	Pork loins	1.1
Butter	11.2	Potatoes	5.9
Cream	1.3	Sugar	11.6
Eggs	2.3	Other items	24.5
Fowl	1.9		

It is interesting that twelve dietary items yield 75 per cent. of the fuel value and that 181 other varieties yield the remaining 25 per cent. Bread, butter, milk, and sugar together yield 50 per cent. of the food fuel.

FOOD REFORM

Rubner[1] has set forth his ideas of true reform with regard to the question of the nourishment of the masses. There should be less profit to middlemen. If food must be eaten outside the home, there should be cheap restaurants or public kitchens where nourishing food can be purchased. It is cheaper to cook in one's own kitchen provided the fire that is used for cooking is needed for heating. The personal ownership of a house and garden to the wide-spread extent of such ownership in America must be morally uplifting for a community. For this reason factories should be built in the country. Furthermore, children are more useful in the country than in the city. The cost of rooms in which to live bears an intimate relation to the amount of money available for food. Not only are quarters costly in the town, but many landlords classify children with cats and dogs as undesirable tenants.

The housewife should know about cooking, and both she and her husband should know something of the value of food. The sum wasted for alcoholic beverages would frequently be sufficient to turn the scale in favor of the proper nutrition of the family. Cheaper milk

[1] Rubner, M.: "Wandlungen in der Volksernährung," Leipzig, 1913.

for the babies of the poor and adequate nourishment for school children are important factors in the situation. Rubner regrets that the knowledge of biology, even among the educated classes, is so limited that the science of nutrition appears to them to be wholly useless.

CONCLUSION

The annual value of food used by the people of the United States is at least $12,000,000,000. This is taken with little knowledge of what food really is. It has been thought by workers in the laboratory that it would be of great importance in times of poverty and distress to associate the caloric value of food with cost in dollars and cents. In the third edition of this book much was said upon this subject which need not here be repeated. Since that writing we have passed through a great crisis. It was a group of men within the Royal Society of London whose policy saved their country in 1917–18. Through the acceptance and support of that policy by the Interallied Scientific Food Commission the allied population of 225,000,000 individuals was maintained in good nutritive condition.

These problems called the scientist from laboratory work on rats, mice, pigeons, cats, dogs, and a few men, and confronted him with affairs of world-wide scope.

Holland and Japan have instituted national laboratories of human nutrition. To a man of large affairs the maintenance at Boston of the Nutrition Laboratory of the Carnegie Institution of Washington, with its budget of $50,000 per annum, appeals impressively to the imagination, yet this work is maintained at an expense of about $\frac{1}{2500}$ of 1 per cent. of what the American people pay for food. To build one battleship requires one thouand times more money than that useful Nutrition Laboratory spends in a year.

As enlightenment grows, let us hope for fewer battleships and better supported laboratories. For, in the words of Alonzo Taylor,

"The future social organization will be the product of the land, the population, the development of the arts and sciences and the standard of living."

Science, Patrie, Humanité, Justice—ce sont de grands mots et de grandes idées aussi; elles peuvent paraître démodées, mais je les chéris aujourd'hui et je les vénère comme au temps de ma lointaine jeunesse. Car ce sont les étoiles étincelantes vers lesquelles nous devons tous deriger notre course.

CHARLES RICHET on his seventy-fifth birthday.

APPENDIX

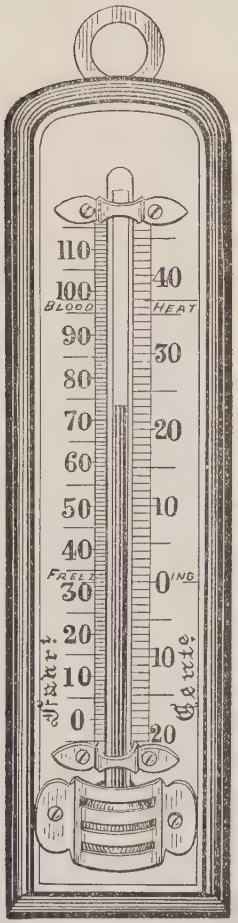


Fig. 46.—Thermometer showing comparison of Fahrenheit and Centrigrade scales.

CONVENIENT COMPARISONS OF METRIC AND AVOIRDUPOIS WEIGHTS

1 kilogram	=	2.2046	pounds
1 pound	=	453.6	grams
1 ounce	=	28.3	grams
1 liter	=	61.027	cubic inches = 1.7608 pints
1 gram-calorie	=	0.425	kilogram-meters of mechanical energy
1 meter	=	3.2809	feet
1 kilometer	=	0.6214	miles

THE CHEMICAL COMPOSITION OF NORMAL URINES ON PURIN-FREE DIETS

(After Folin, see p. 251)

	Person						
	E. S. A.		H. B. H.				
	June		March			July	
	29th	30th	8th	9th	10th	13th	20th
Total N in grams	14.6	15.8	15.9	15.5	15.0	16.8	3.6
Urea N	12.6	13.9	13.5	13.4	12.9	14.7	2.2
Ammonia N	0.54	0.54	0.41	0.41	0.43	0.49	0.42
Creatinin N	0.39	0.43	0.70	0.64	0.69	0.58	0.60
Uric Acid N	0.15	0.11	0.26	0.23	0.27	0.18	0.09
Undetermined N	0.96	0.88	1.06	0.79	0.68	0.85	0.27
Total SO_3 in grams	3.02	2.94	3.03	2.49	2.19	3.64	0.76
Inorganic SO_3	2.56	2.58	2.48	2.05	1.74	3.27	0.46
Ethereal SO_3	0.26	0.22	0.20	0.18	0.19	0.19	0.10
Neutral SO_3	0.20	0.14	0.35	0.26	0.26	0.18	0.20
In per cent. of total N:							
Urea N	86.0	87.7	84.7	86.4	86.2	87.5	61.7
Ammonia N	3.6	3.3	2.6	2.7	2.9	3.0	11.3
Creatinin N	2.7	2.7	4.4	4.1	4.6	3.6	17.2
Uric Acid N	1.0	0.7	1.6	1.7	1.8	1.05	2.5
Undetermined N	6.6	5.6	6.7	5.1	4.4	4.85	7.3
In per cent. of total SO_3:							
Inorganic SO_3	84.7	87.7	81.8	82.0	79.4	90.0	60.5
Ethereal SO_3	8.6	7.4	6.6	7.2	8.6	5.2	13.2
Neutral SO_3	6.7	4.9	11.6	10.8	12.0	4.8	26.5

For the chemical analysis of foods and their caloric values consult the valuable "Chemical Composition of American Food Materials," by Atwater, W. O., and Bryant, A. P.: Bull. 28 (Revised), U. S. Depart. Agriculture, Washington, D. C., 1906.

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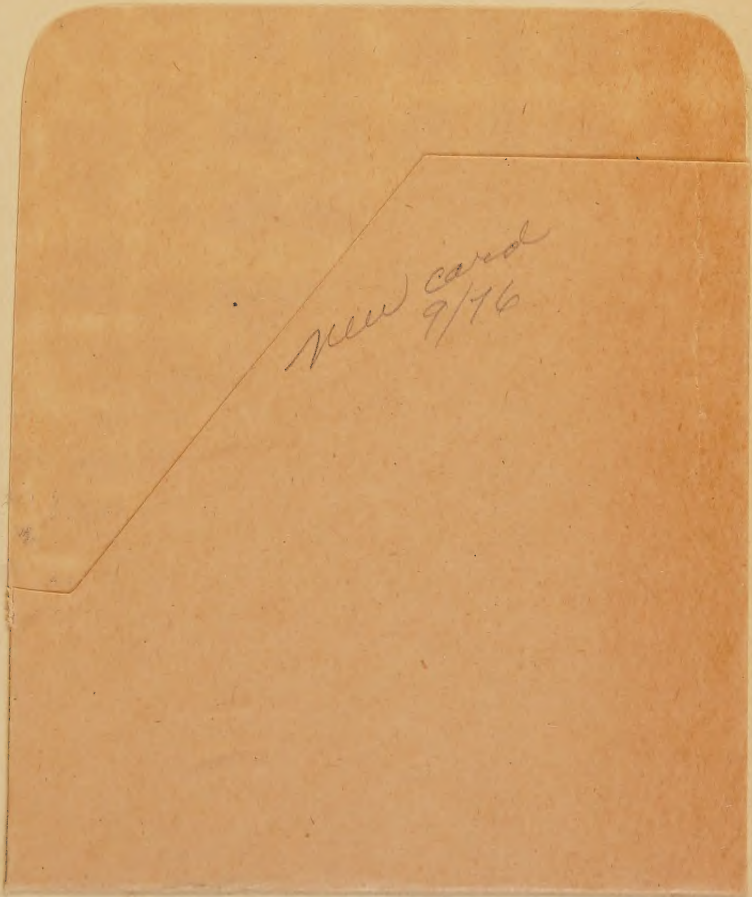
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